Hospital Universitario
JUAN RAMÓN JIMÉNEZ

HP: influencia de las nuevas guías en el manejo farmacológico.

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22 de Febrero de 2024

XII CONGRESO DE AADEA

ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–114
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ESC/ERS GUIDELINES

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

Authors/Task Force Members: Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M.F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J.S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), Marion Delcroix *† (ERS Chairperson) (Belgium), Stephan Rosenkranz *† (ESC Chairperson) (Germany), and ESC/ERS Scientific Document Group

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
M. HUMBERT ET AL.

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Marc Humbert[1,2], Gabor Kovacs[3,4], Marius M. Hoeper[5,6], Roberto Badagliacca[7,8], Rolf M.F. Berger[9], Margarita Brida[10,11], Jørn Carlsen[12,13], Andrew J.S. Coats[14,15], Pilar Escribano-Subias[16,17,18], Pisana Ferrari[19,20], Diogenes S. Ferreira[21], Hossein Ardeschir Ghofrani[22,23,24], George Giannakoulas[25], David G. Kiely[26,27,28], Eckhard Mayer[29], Gergely Meszaros[19,30], Blin Nagavci[31], Karen M. Olsson[32], Joanna Pepke-Zaba[33], Jennifer K. Quint[34], Göran Rådegran[35,36], Gerald Simonneau[37,38], Olivier Sitbon[2,37,39], Thomy Tonia[40], Mark Toshner[41], Jean-Luc Vachiery[42], Anton Vonk Noordegraaf[43], Marion Delcroix[44,46], Stephan Rosenkranz[45,46] and the ESC/ERS Scientific Document Group

Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

Definición.

TABLE 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Eur Respir J 2022; in press: 2200879

Clasificación HP.

GROUP 1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 2 PH associated with left heart disease
- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction[b]
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia
- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions
- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions[c]

GROUP 5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

Eur Respir J 2022; in press: 2200879

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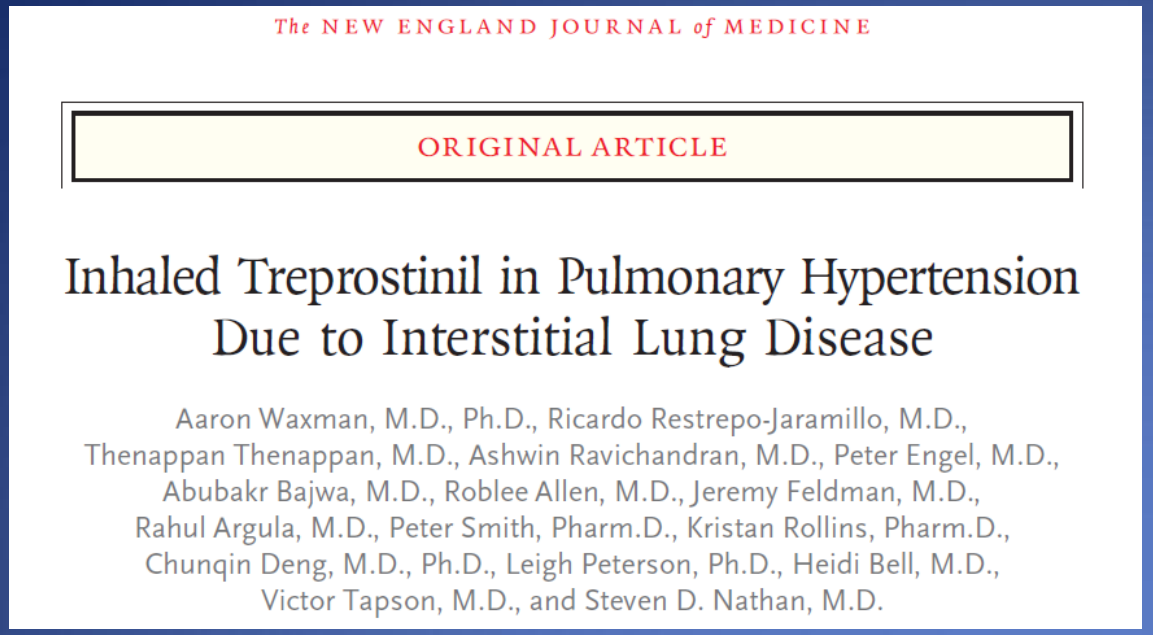
HP asociada a neumopatía.

En pacientes con neumopatía y sospecha de HP, se recomienda optimizar el tratamiento de la enfermedad de base, AOS, oxigenoterapia, Rehabilitación,	I	C
En pacientes con neumopatía e HP grave, se recomienda un enfoque terapéutico individualizado	I	C
Treprostinil inhalado puede ser considerado en pacientes con HP asociada a EPID.	IIb	B
Ambrisentán y Riociguat no están recomendados en HP asociada a EPID.	III	B
El uso de fármacos para la HAP no está recomendado en pacientes con neumopatía e HP no grave	III	C
El uso de IFD-5 puede ser considerado en pacientes con HP grave asociada a EPID	IIb	C
El uso de IFD-5 no está recomendado en pacientes con EPID e HP no grave	III	C

Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

INCREASE CLINICAL TRIAL. N Engl J Med 2021;384:325-34.

- 326 pacientes randomizados 1:1. 47% mujeres.
- Objetivo primario: cambio en distancia recorrida en TM6M a las 16 semanas.
- Diagnóstico:
  - EPID por TAC al menos 6 meses
  - HP por CCD al menos 1 año: PAPm>25 mmHg, PCP <15 mmHg, RVP > 3 UW
  - Si ETC (22% pacientes incluidos) -> FVC < 70%

Treprostinil inh en EPID

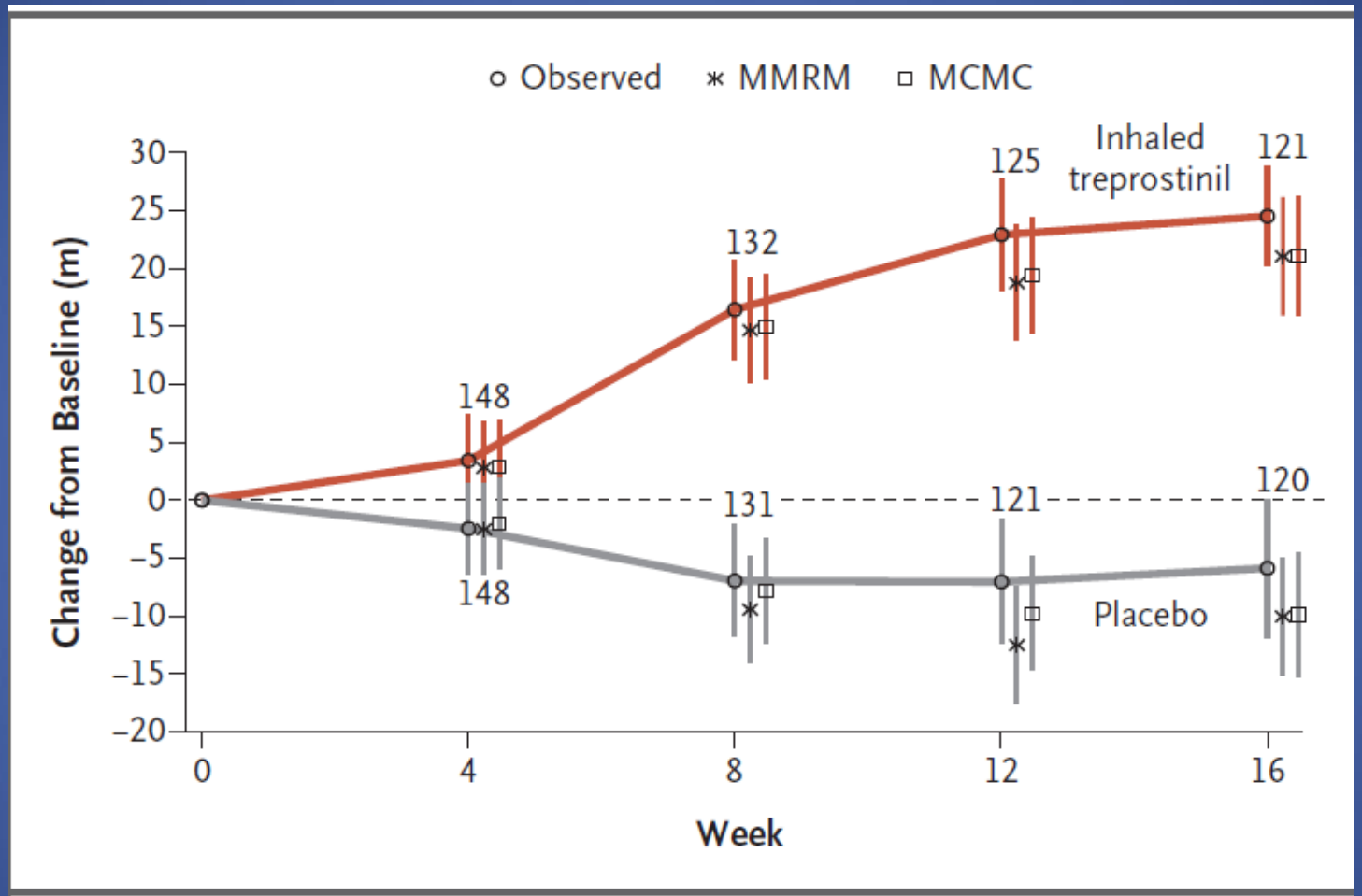


Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

INCREASE CLINICAL TRIAL. N Engl J Med 2021;384:325-34.

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Eur Respir J 2022; in press: 2200879

TABLE 1 Criteria favouring group 1 *versus* group 3 pulmonary hypertension (PH)#

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
Extent of lung disease		
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan¶	Characteristic airway and/or parenchymal abnormalities
Haemodynamic profile		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
Ancillary testing		
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in P_{aCO_2} during exercise	Cardiopulmonary exercise test+ (P_{aCO_2} particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in P_{aCO_2} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Eur Respir J 2018; in press [https://doi.org/10.1183/13993003.01914-2018].

Tratamiento HAP. Medidas generales

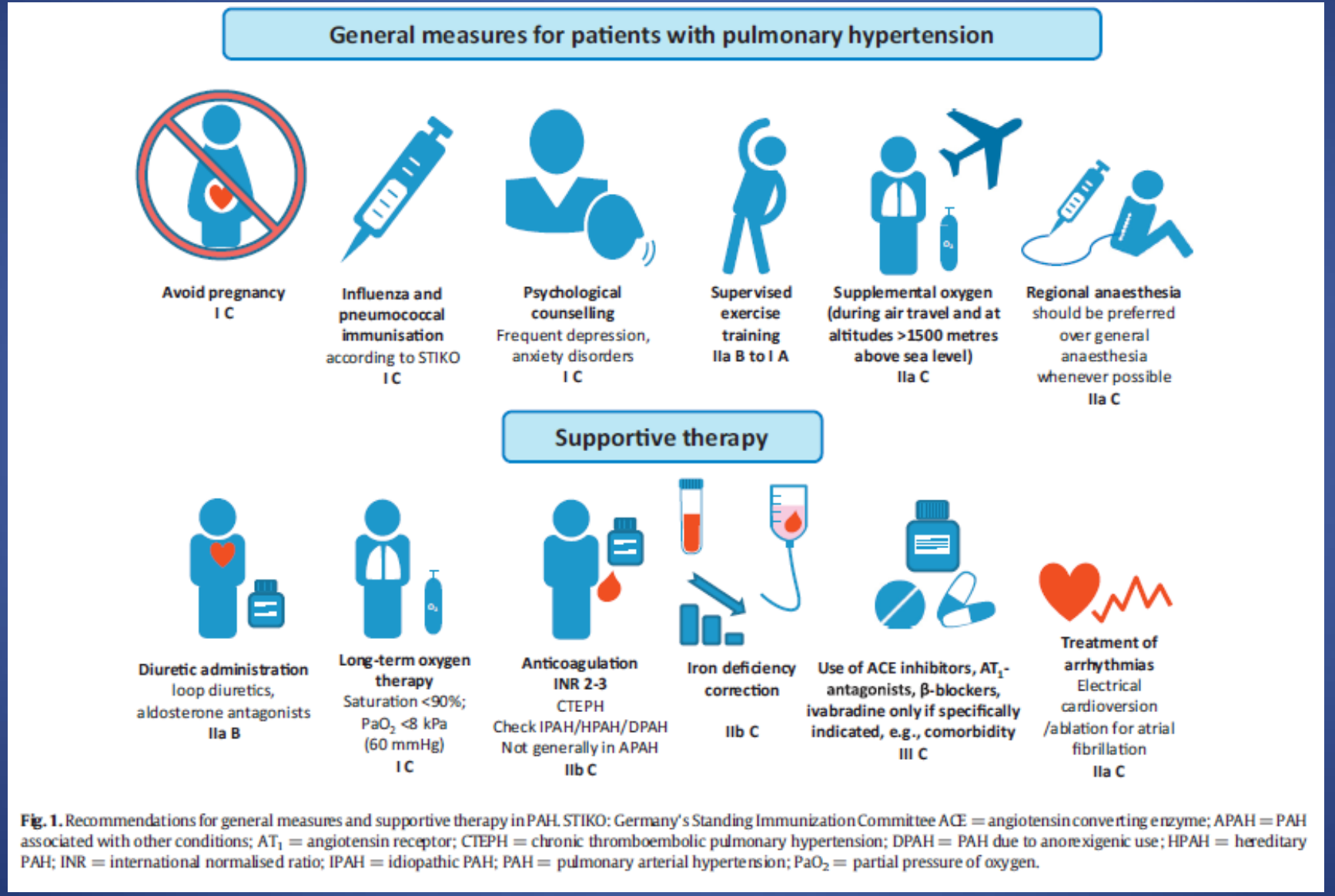
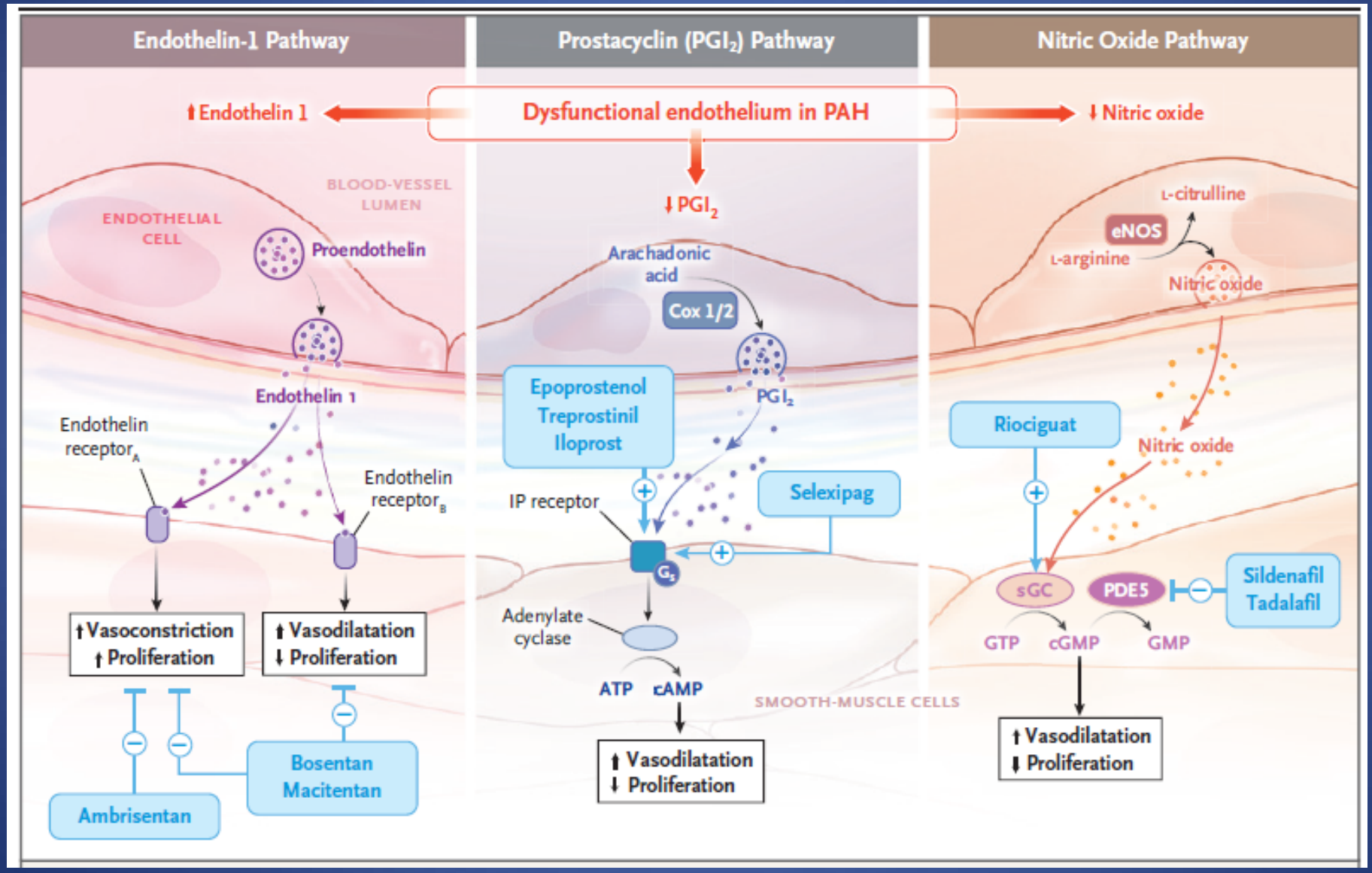


Fig. 1. Recommendations for general measures and supportive therapy in PAH. STIKO: Germany's Standing Immunization Committee ACE = angiotensin converting enzyme; APAH = PAH associated with other conditions; AT_1 = angiotensin receptor; CTEPH = chronic thromboembolic pulmonary hypertension; DPAH = PAH due to anorexigenic use; HPAH = hereditary PAH; INR = international normalised ratio; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PaO_2 = partial pressure of oxygen.

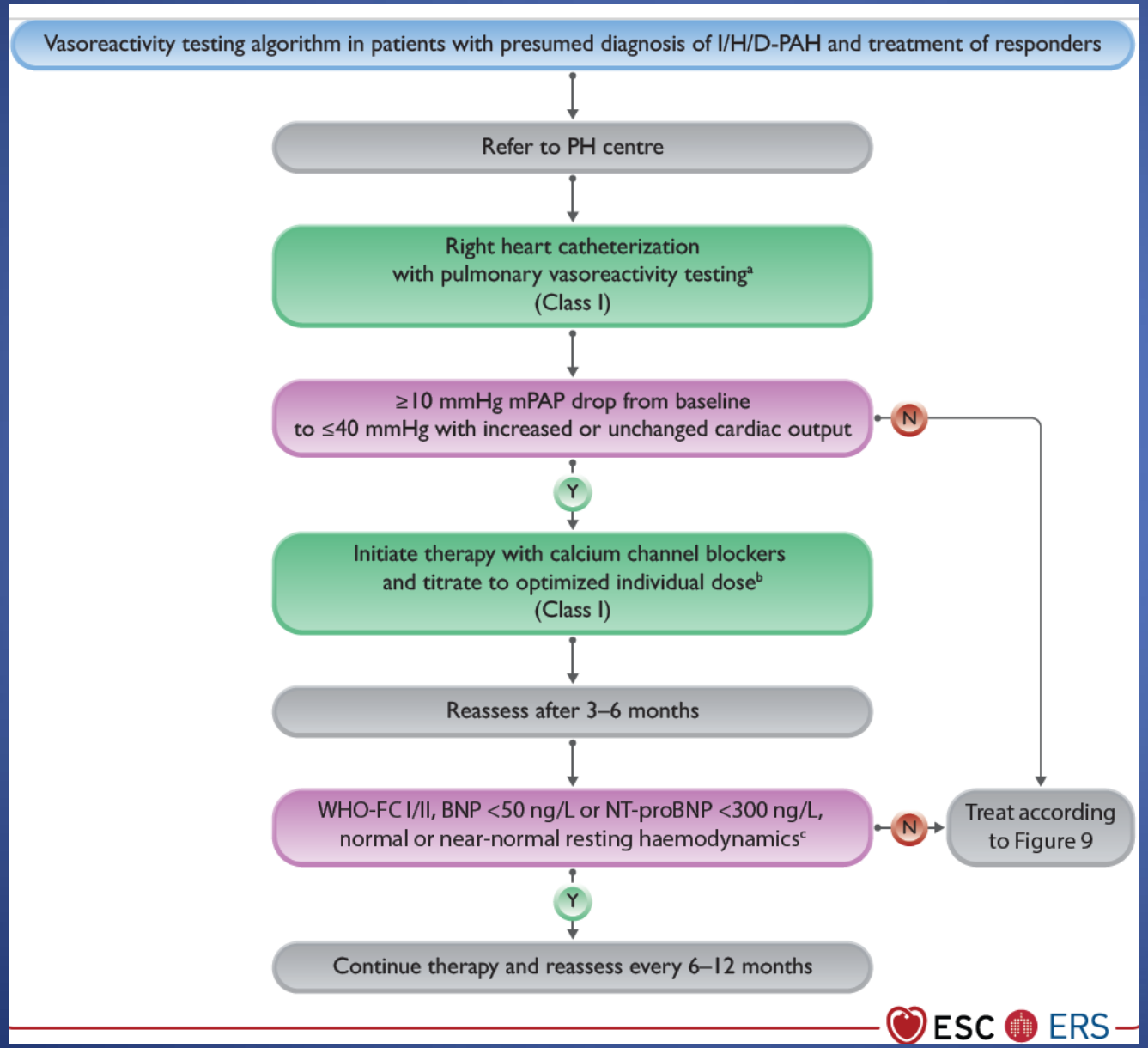
Cologne Consensus Conference 2018. International Journal of Cardiology 2018 In Press

Tratamiento HAP. Vías de tratamiento.



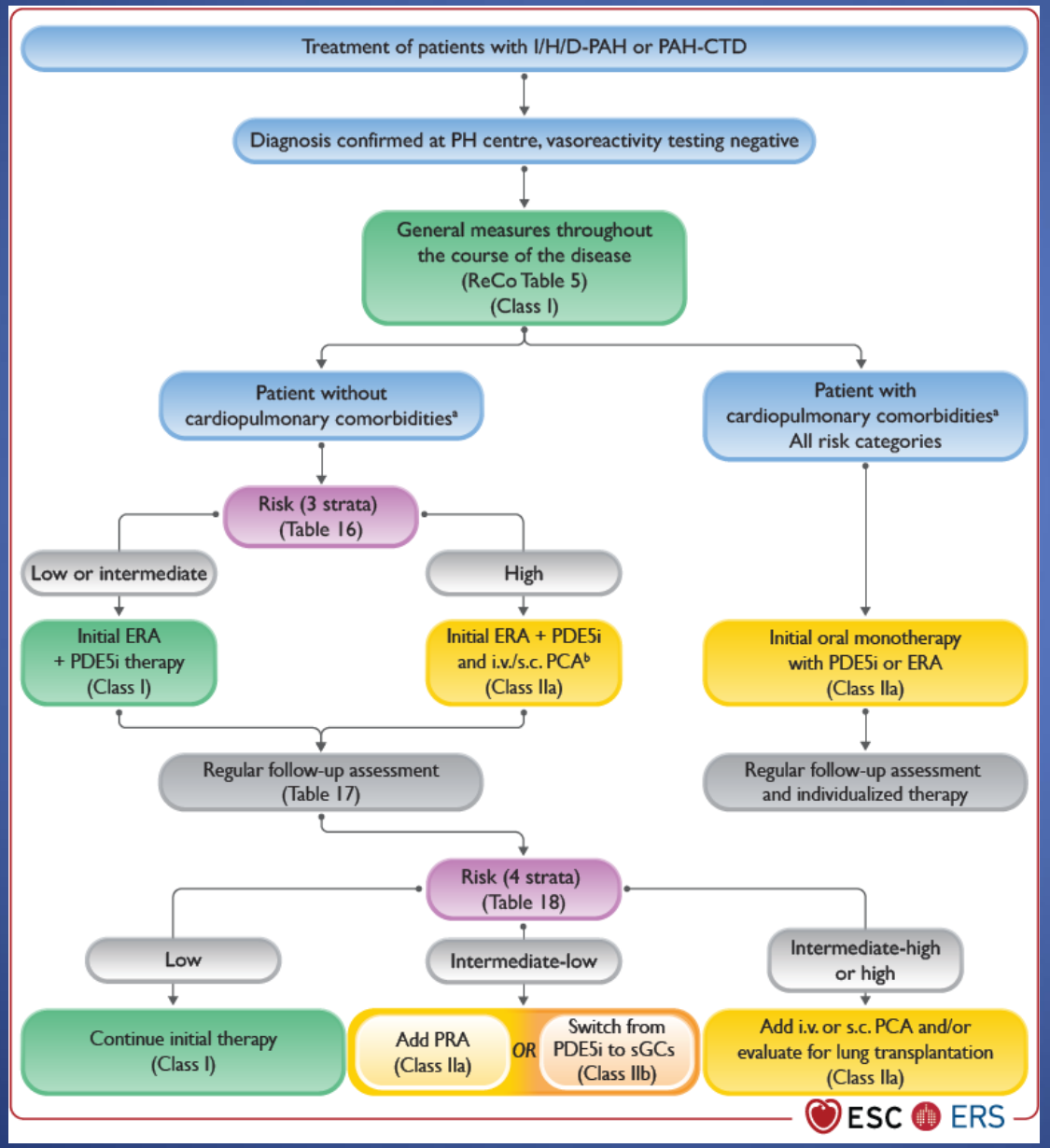
Hassoun PM. N Engl J Med 2021;385:2361-76.

Algoritmo tratamiento TVRP positivo: HAPI/H/D.



Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

Algoritmo tratamiento HAP.



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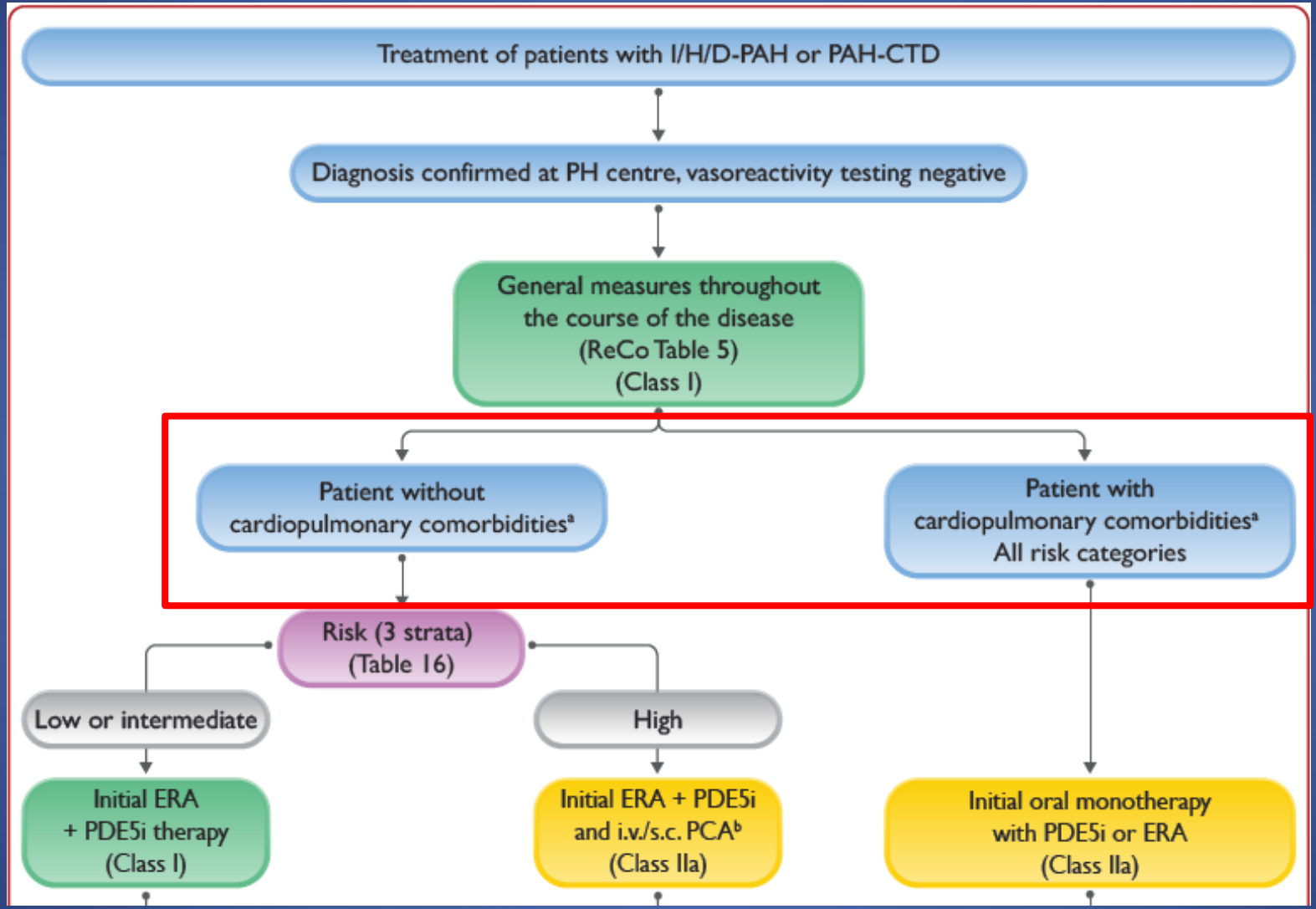
Algoritmo tratamiento HAP.



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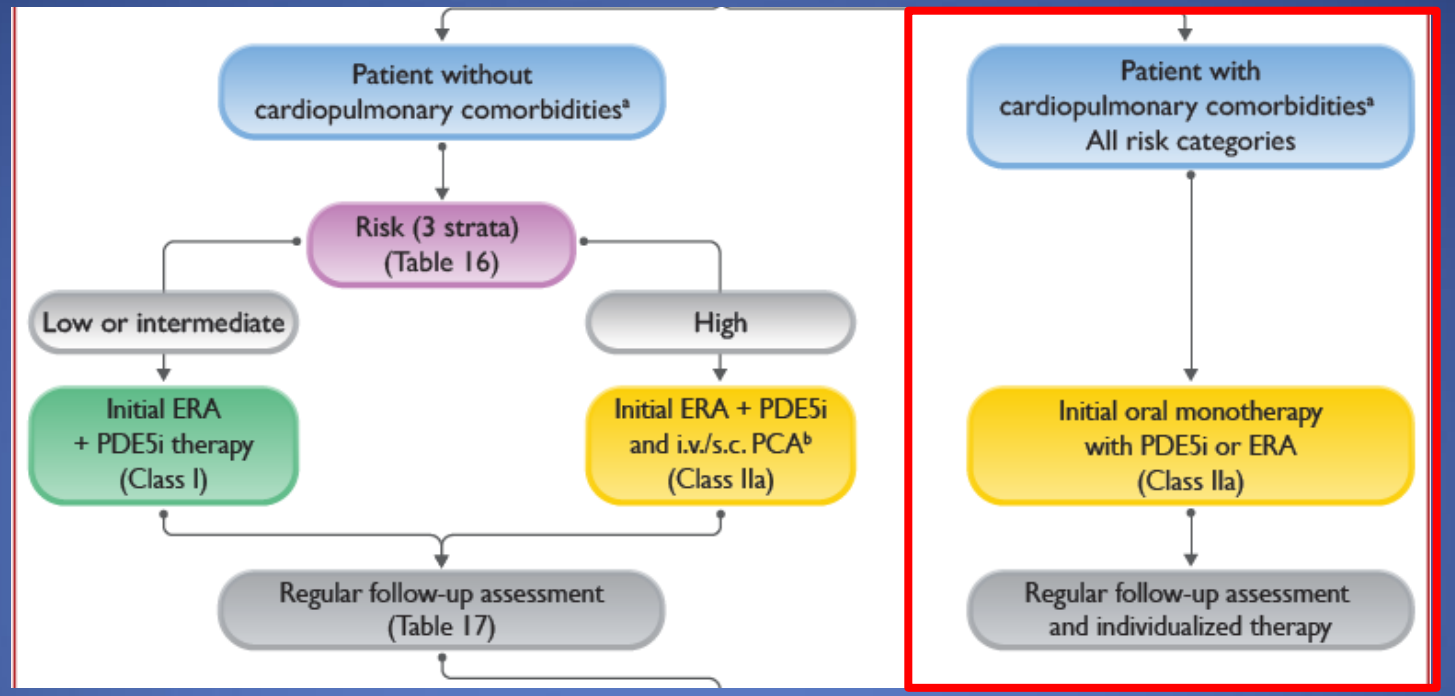
Algoritmo tratamiento HAP.



Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease.

Pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO (<45% of the predicted value).

Eur Respir J 2022; in press: 2200879
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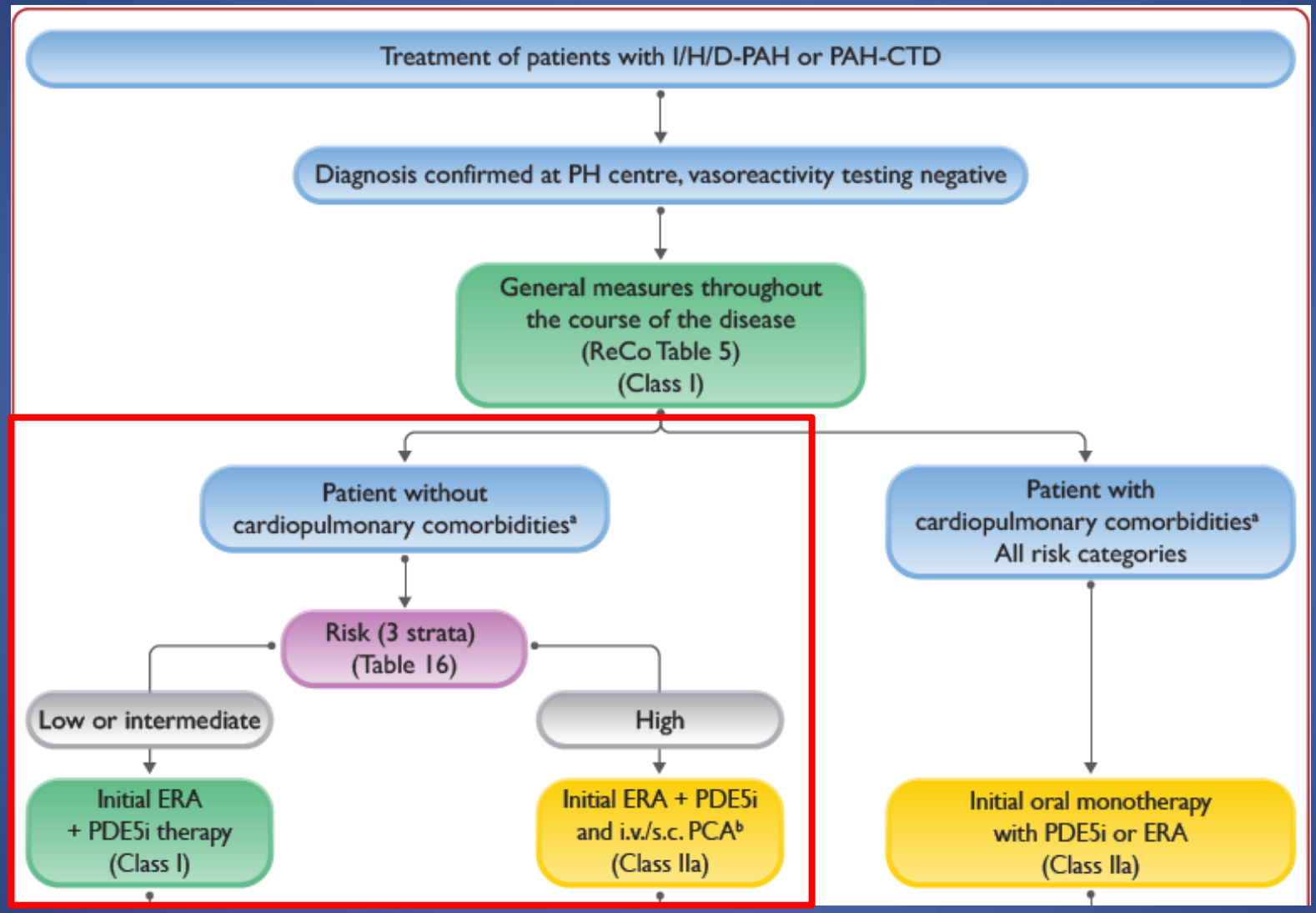
Algoritmo tratamiento HAP.



Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

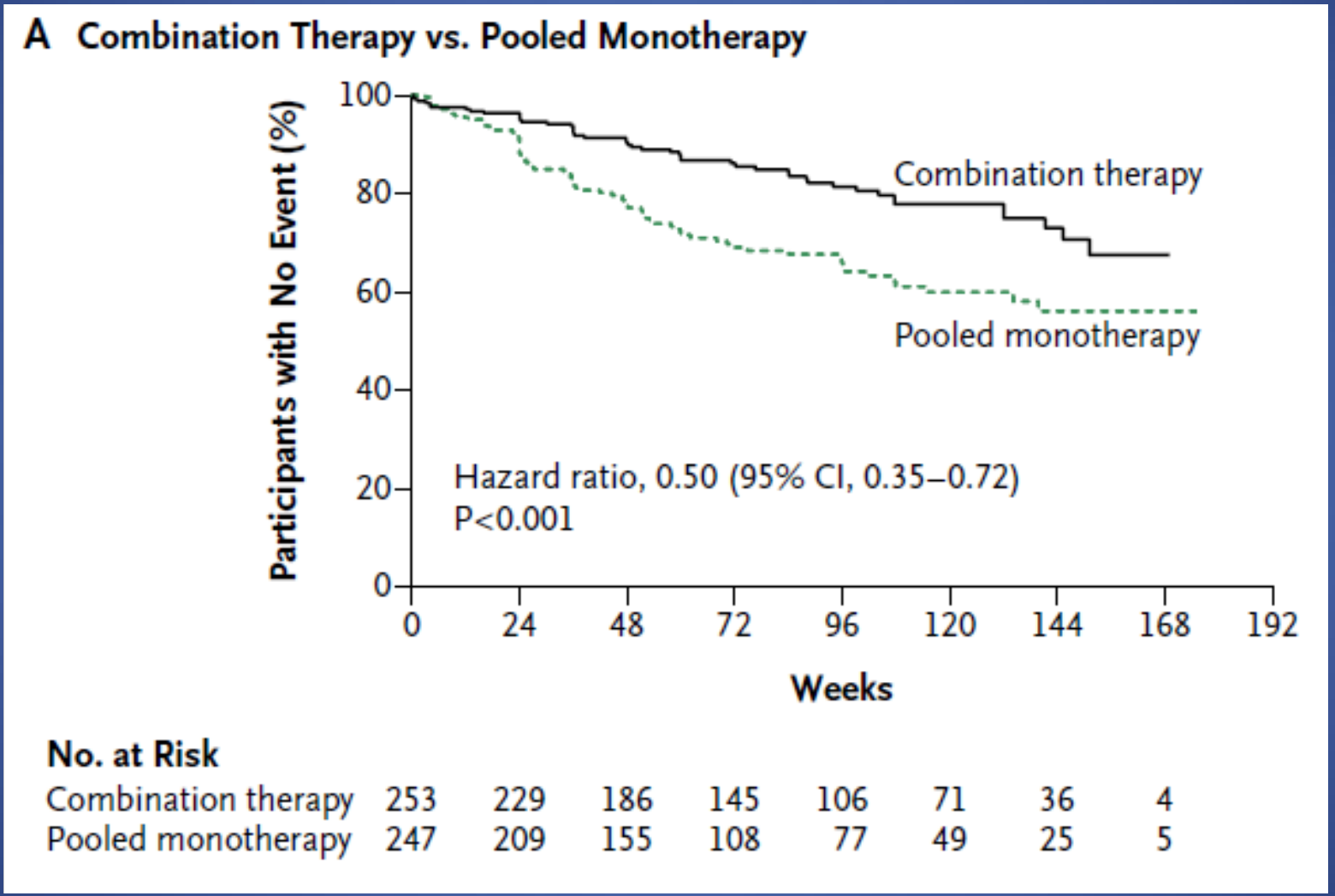
Estratificación pronóstica 3 niveles.

Evaluación del riesgo en la Hipertensión Arterial Pulmonar (modelo 3 niveles)

Factores pronósticos (mortalidad a 1 año)	Riesgo bajo (<5%)	Riesgo intermedio (5-20%)	Riesgo alto (>20%)
Signos clínicos de ICD	Ausentes	Ausentes	Presentes
Progresión de los síntomas	No	Lenta	Rápida
Síncope	No	Ocasional	Repetido
Clase funcional OMS	I, II	III	IV
Distancia recorrida en TM6M	>440m	165-440m	<165m
Prueba de esfuerzo cardiopulmonar	VO_2pico >15mL/kg/min (>65% ref.) VE/VCO2<36	VO_2pico 11-15mL/kg/min (35-65% ref.) VE/VCO2 36-44,9	VO_2-pico<11mL/kg/min (<35% ref.) VE/VCO2≥45
BNP o NT-proBNP	BNP<50ng/L NT-proBNP<300ng/L	BNP 50-800ng/L NT-proBNP 300-1.100ng/L	BNP>800ng/L NT-proBNP>1.100ng/L
Ecocardiografía	Área AD<18cm2 TAPSE/PAPs >0.32 mm/mmHg No derrame pericárdico	Área AD 18-26cm2 TAPSE/PAPs 0.19–0.32 mm/mmHg Mínimo derrame pericárdico	Área AD>26cm2 TAPSE/PAPs <0.19 mm/mmHg Moderado o grave derrame pericárdico
Resonancia magnética cardiaca	RVEF > 54% SVI > 40 mL/m^2 RVESVI < 42 mL/m2	RVEF 37–54% SVI 26-40 mL/m^2 RVESVI 42-54 mL/m2	RVEF ,37% SVI < 26 mL/m^2 RVESVI >54 mL/m2
Hemodinámica	PAD<8mmHg IC≥2,5L/min/m2 SvO2>65% SVI > 38mL/m^2	PAD 8-14mmHg IC 2,0-2,4L/min/m2 SvO2 60-65% SVI 31-38mL/m^2	PAD>14mmHg IC<2,0L/min/m2 SvO2<60% SVI < 31mL/m^2

Modificado Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2022.

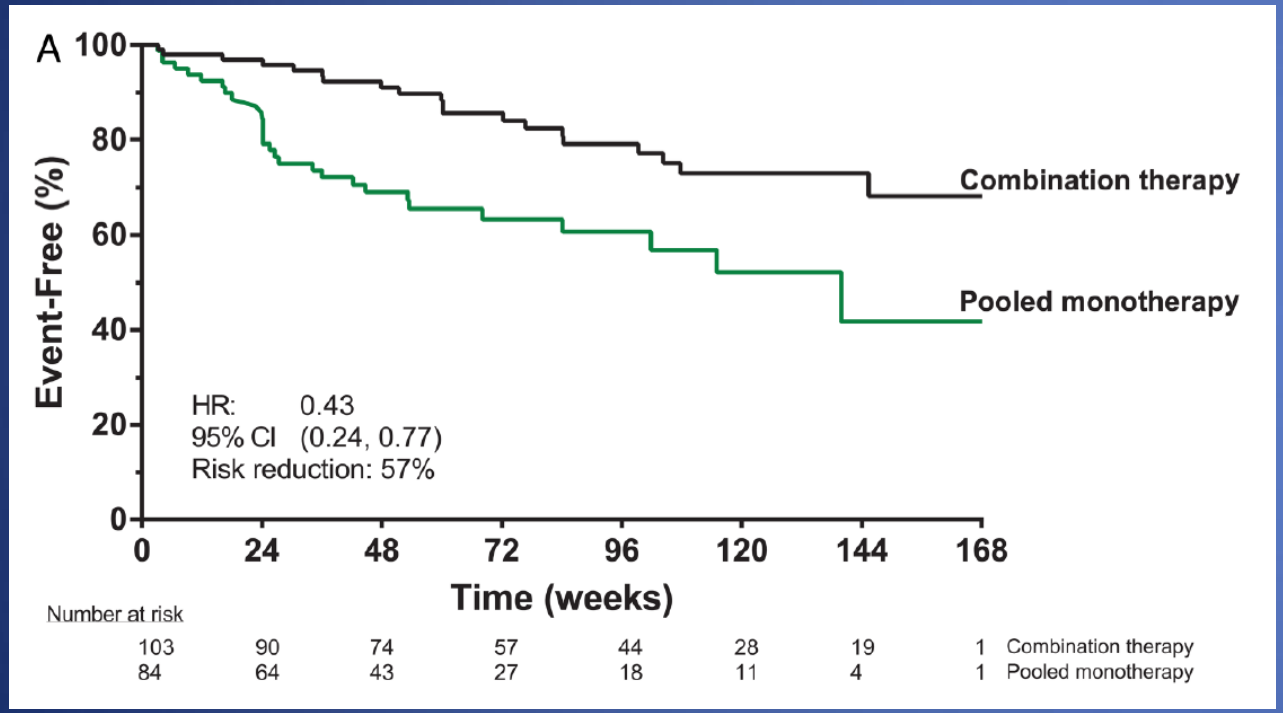
Riesgo bajo-intermedio. Combinada oral de inicio. AMB+TAD



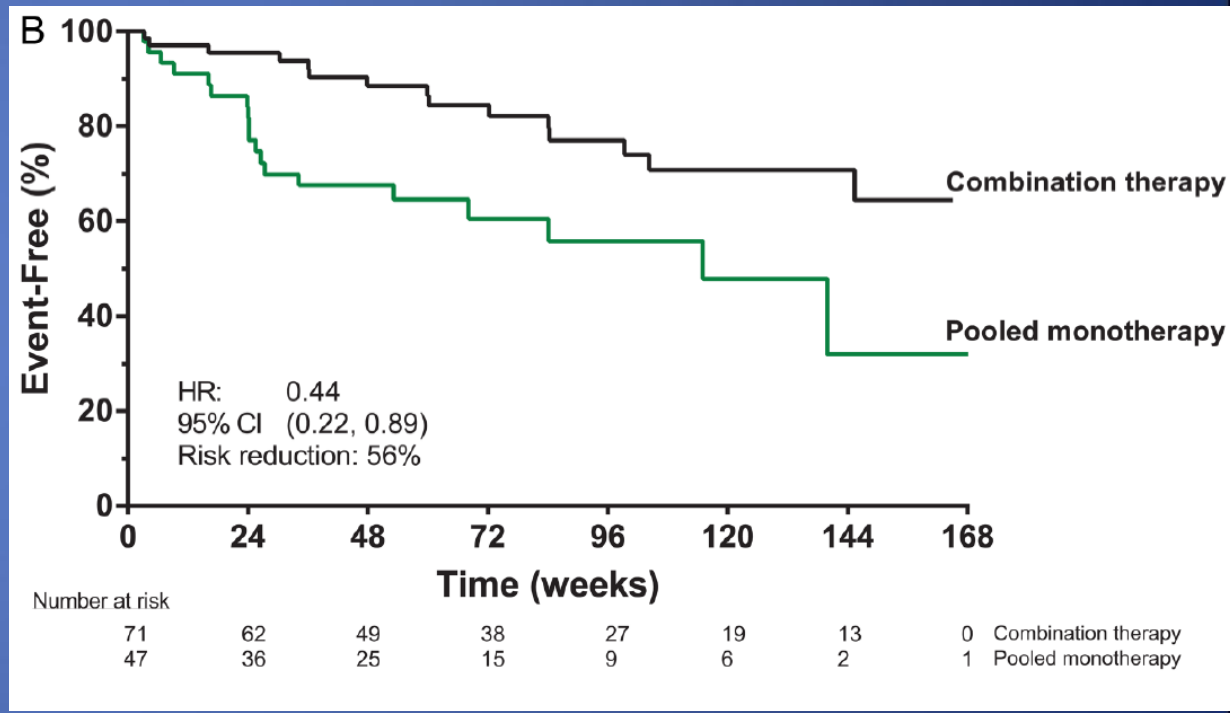
N Engl J Med 2015;373:834-44.

Riesgo bajo-intermedio. Combinada oral de inicio. AMB+TAD

Conectivopatía



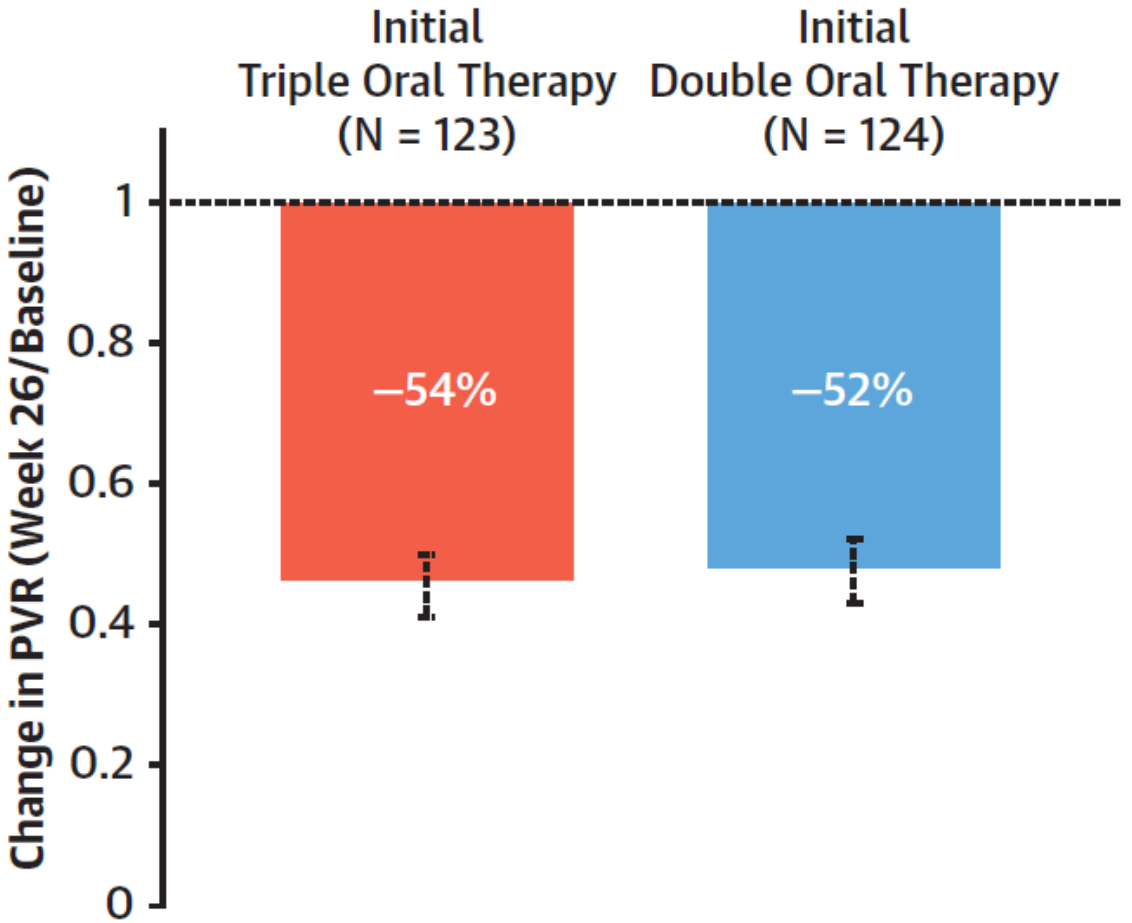
Esclerodermia



Ann Rheum Dis 2016;0:1–9.

Riesgo bajo-intermedio. Combinada oral de inicio. MAC+TAD

FIGURE 2 Change in Pulmonary Vascular Resistance From Baseline to Week 26



J Am Coll Cardiol 2021;78:1393–1403.

Riesgo Alto. Combinada triple de inicio.

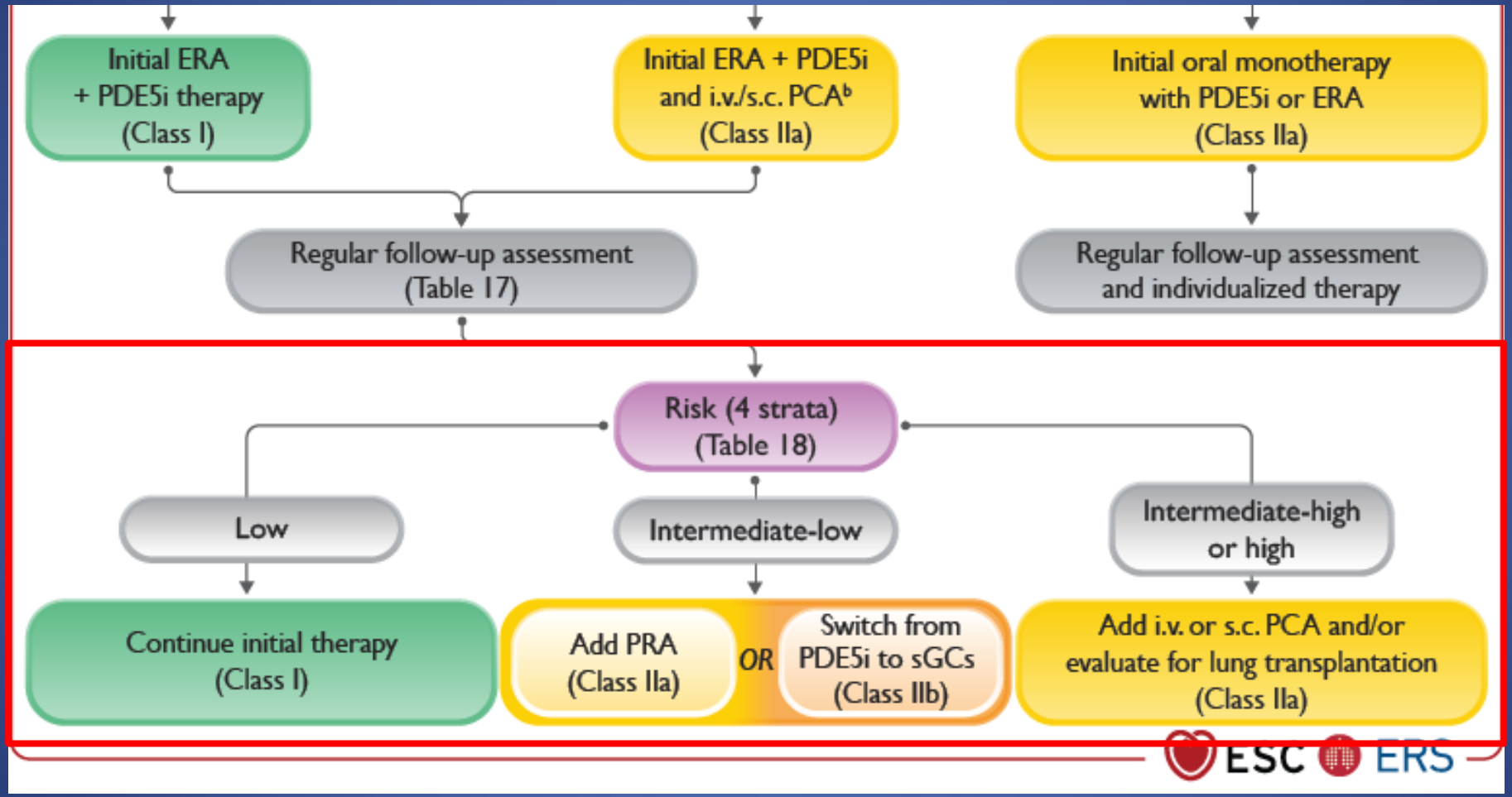
Upfront triple terapia: sildenafilo, bosentán y epoprostenol iv

TABLE 2 Functional class, 6-min walk distance (6MWD) and haemodynamics at the baseline, month 4 and final follow-up visits

	Baseline	Month 4 visit	Final follow-up visit#
NYHA FC I/II/III/IV n	0/0/8/10	1/16/1/0**	4/14/0/0**
6MWD m	227±171	463±94**	514±105**,¶
Haemodynamics			
RAP mmHg	11.9±5.2	4.9±4.9**	5.2±3.5**
mPAP mmHg	65.8±13.7	45.7±14.0**	44.4±13.4**
PCWP mmHg	8.4±3.5	6.7±3.2	7.9±2.8
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	1.66±0.35	3.49±0.69**	3.64±0.65**
PVR $dyn \cdot s \cdot cm^{-5}$	1718±627	564±260**	492±209**
Mean BP mmHg	92.1±12.5	80.1±11.7**	84.9±19.4
HR beats per min	92.3±10.7	83.9±9.8**	79.9±13.4**
$S_{v}O_{2}$ %	51.0±8.5	69.7±5.2**	72.2±4.0**
Dose of epoprostenol achieved $ng \cdot kg^{-1} \cdot min^{-1}$	0	15.9±1.9	19.6±6.0

Eur Respir J 2014; 43: 169

Algoritmo tratamiento HAP.



Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

Estratificación pronóstica: 4 niveles.

Table 18 Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
[a]WHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

Eur Respir J 2022; in press: 2200879
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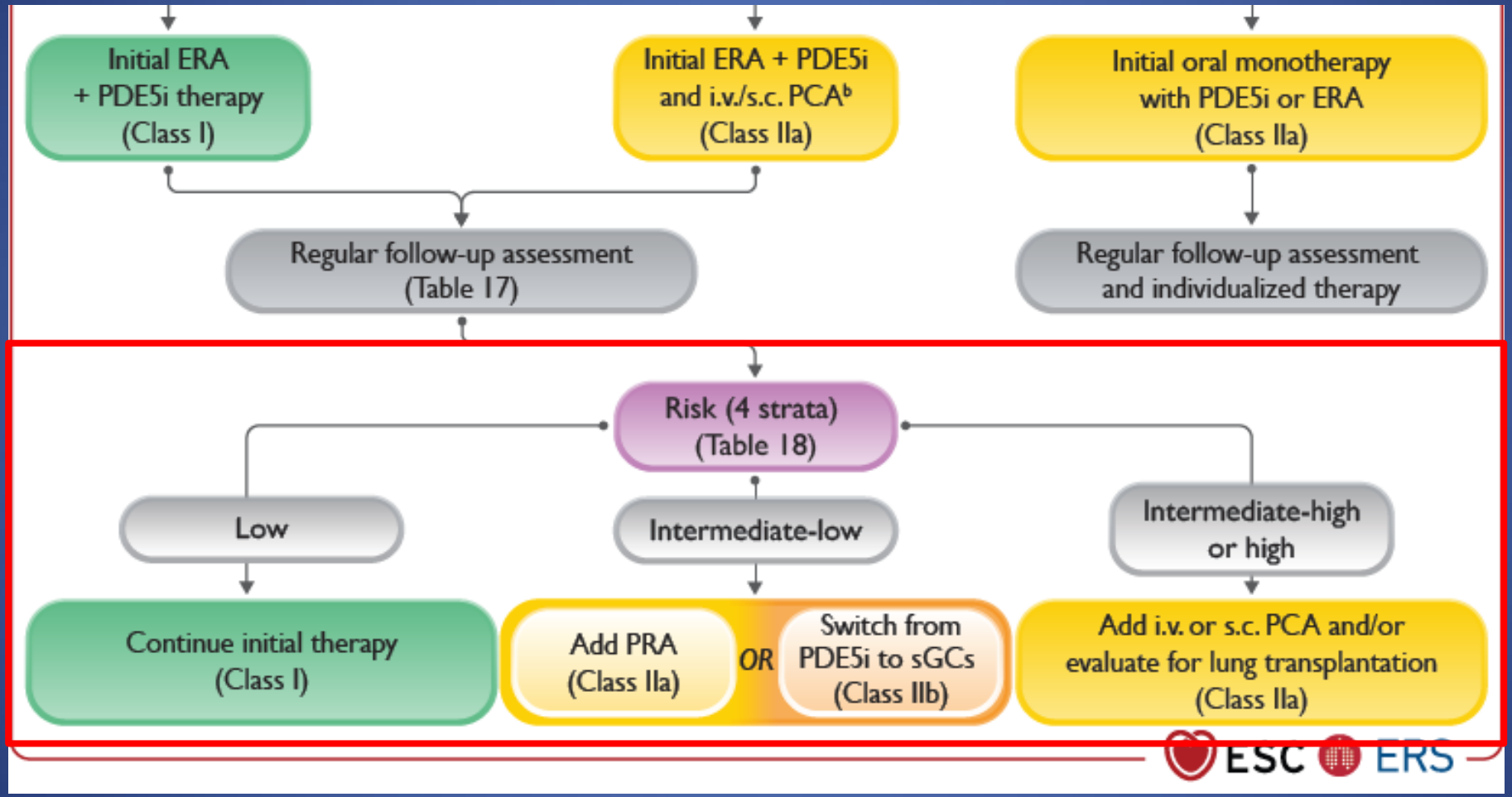
Algoritmo tratamiento HAP.



Eur Respir J 2022; in press: 2200879
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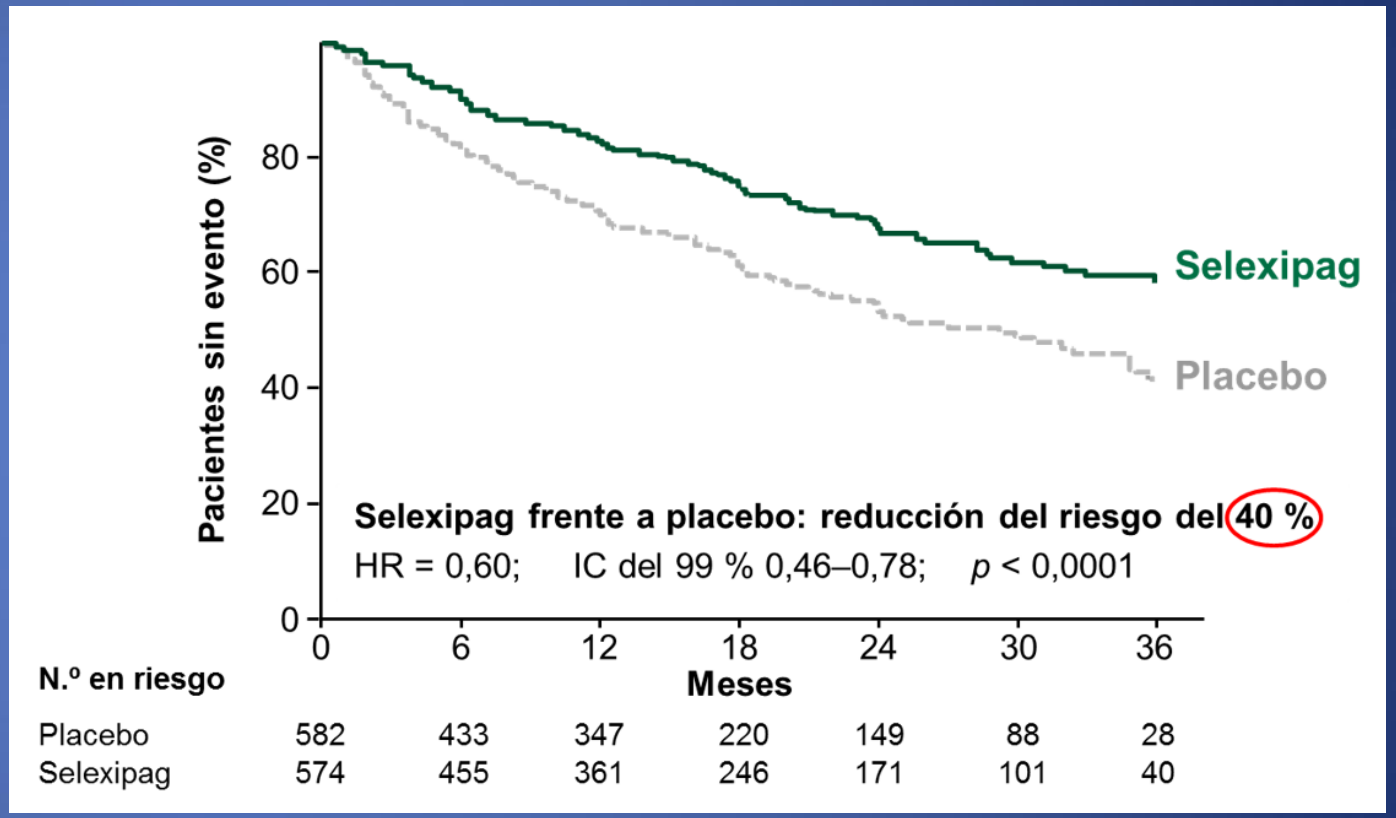
Tratamiento HAP. Triple terapia secuencial. GRIPHON.

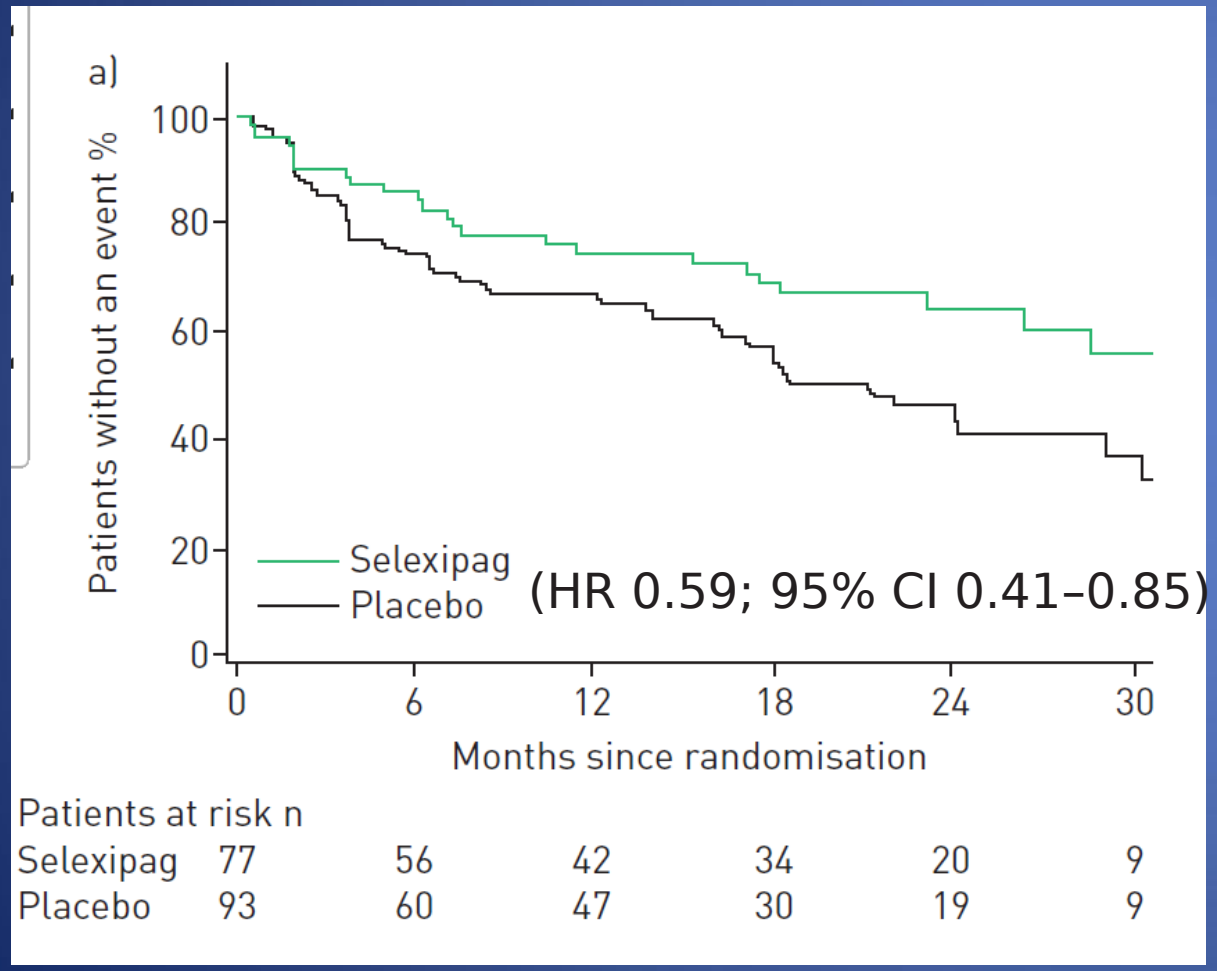
- Agonista de receptores IP de prostaciclinas. Vía oral.
- Mejoría de morbimortalidad en CF II-III como terapia secuencial
- Bien tolerado, trastornos gastrointestinales y cefalea.
- Dosis máxima 1600 µg/12h



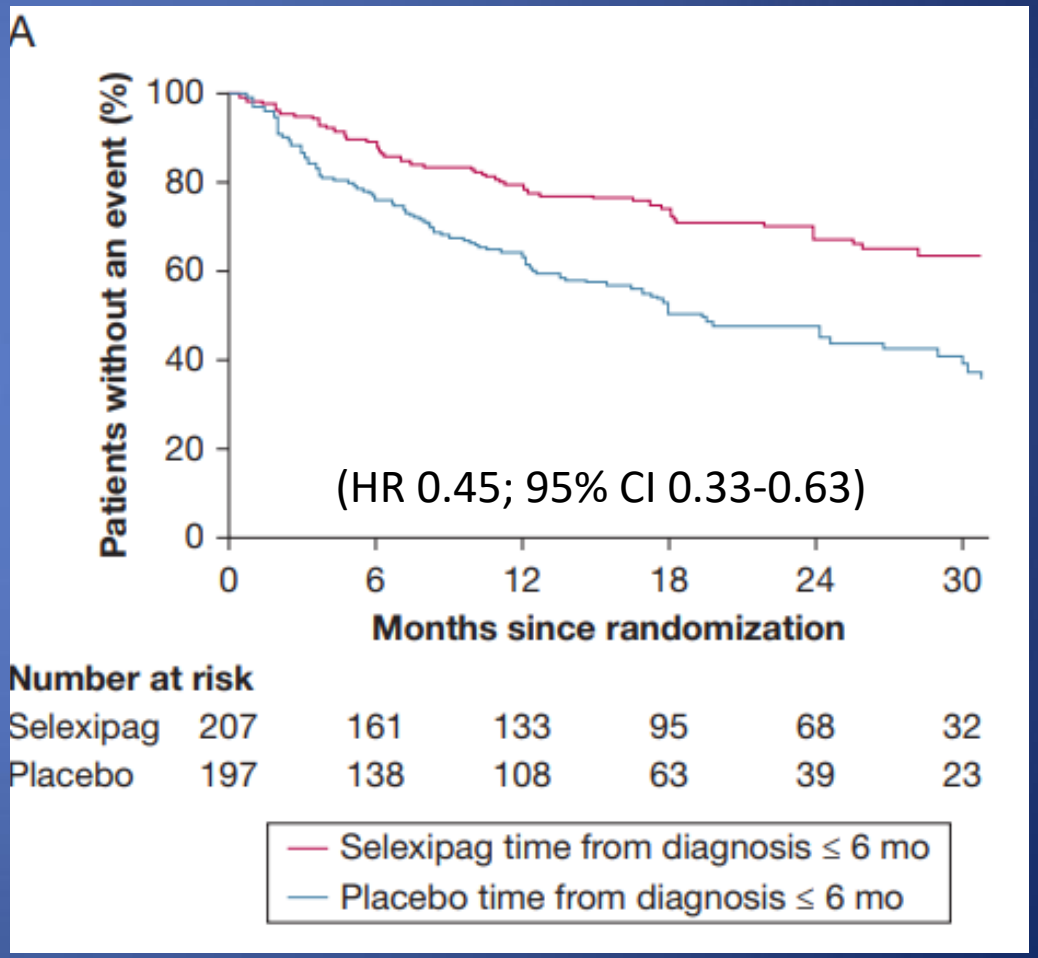
Sitbon O, *et al. New Engl J Med* 2015; 373:2522-33.

Tratamiento HAP. Triple terapia secuencial. GRIPHON.

Esclerosis sistémica

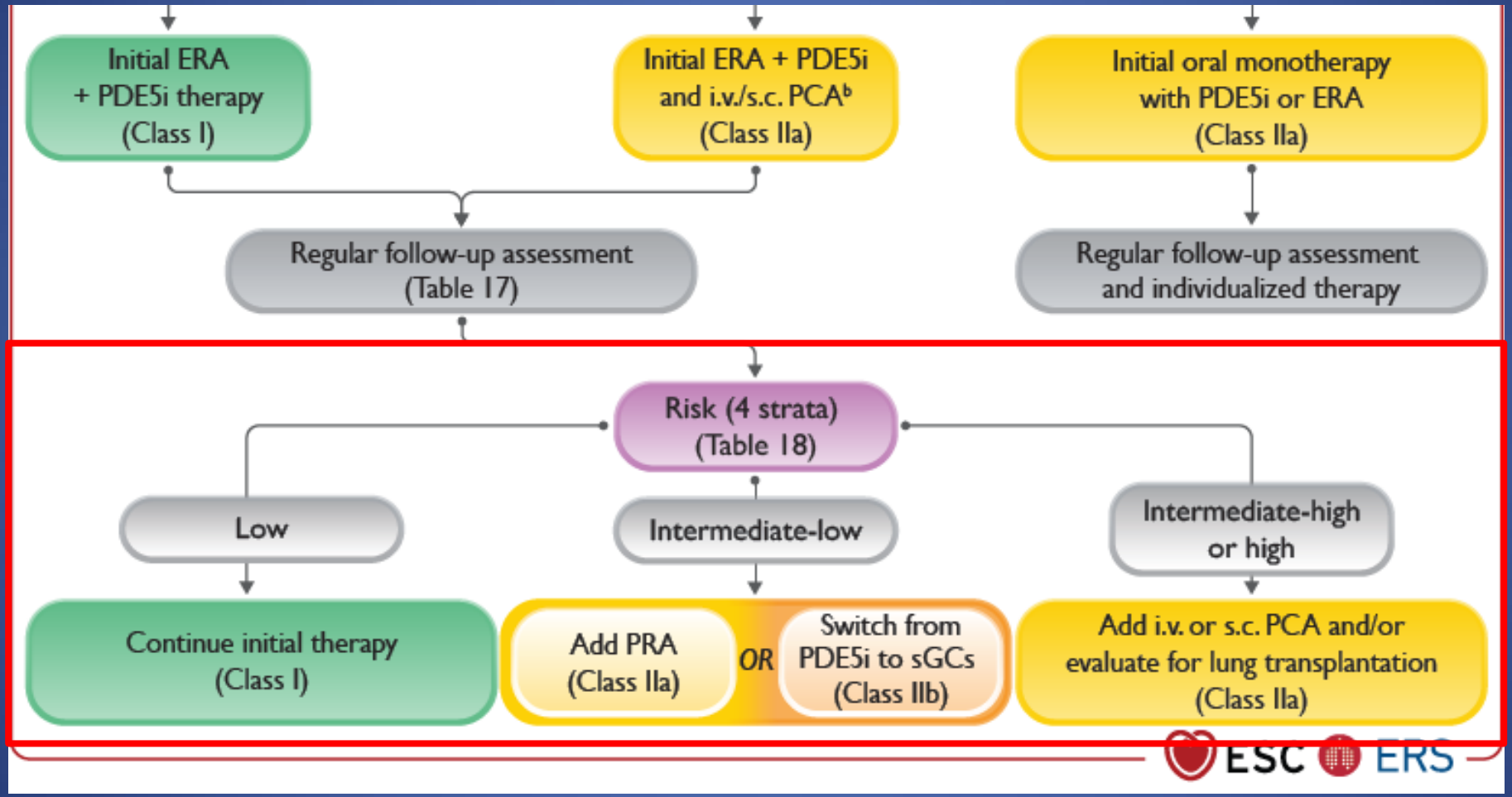


Eur Respir J 2017; 50: 1602493



CHEST 2021; 160(1):277-286

Algoritmo tratamiento HAP.



Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

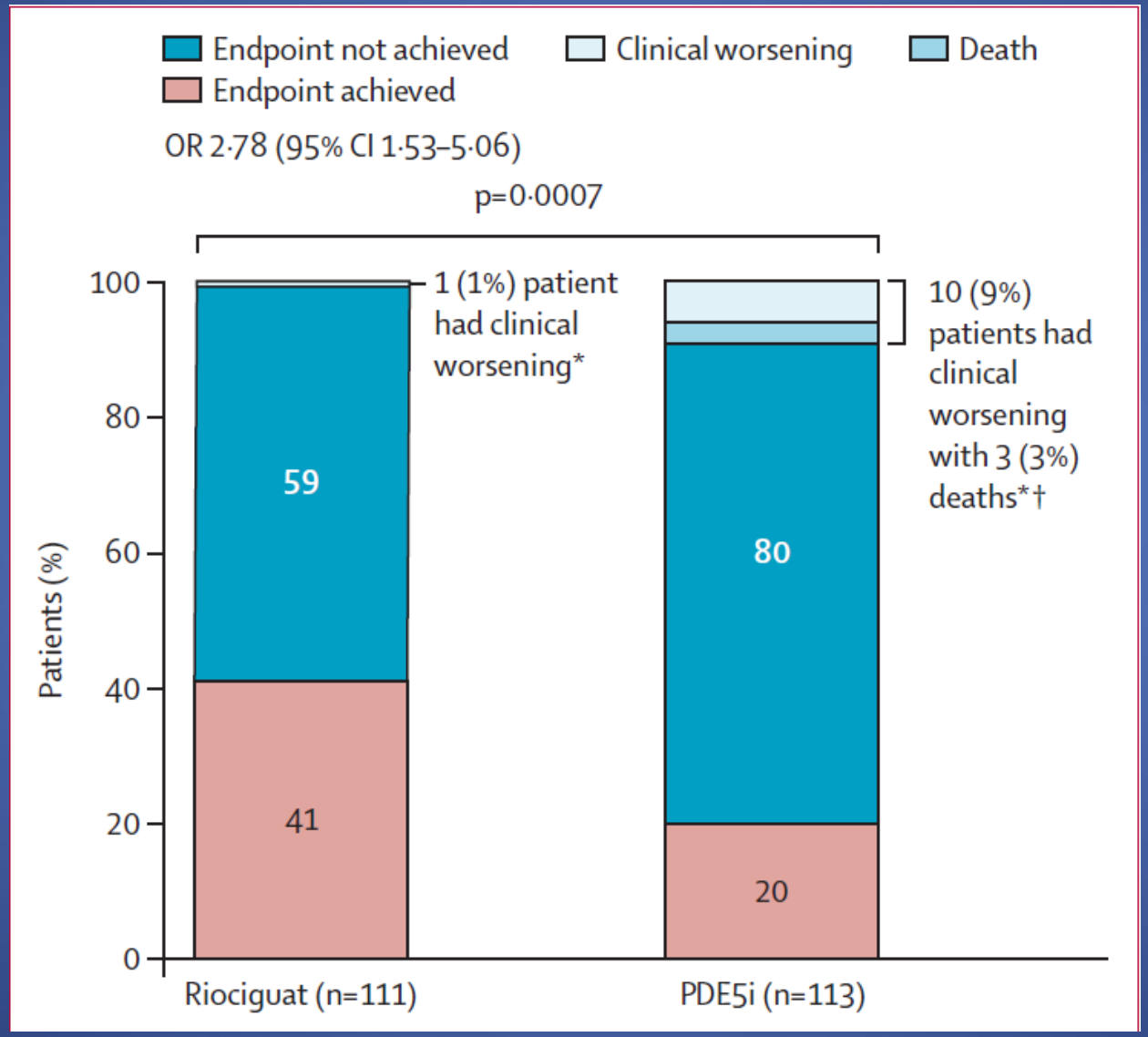
Tratamiento HAP. Switch tratamiento. REPLACE

Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial

***Lancet Respir Med* 2021**

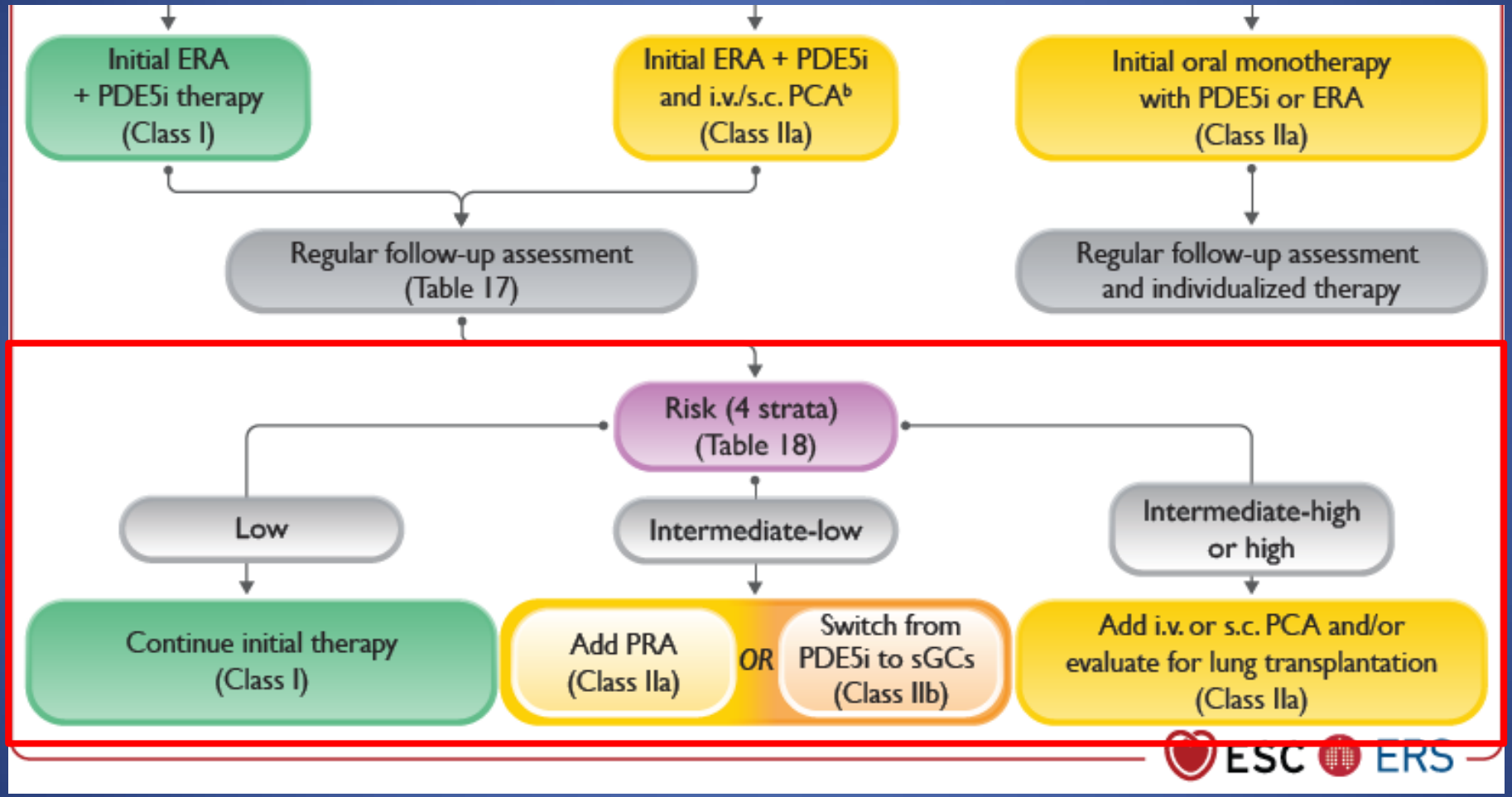
- 226 pacientes con HAP en tratamiento con IFD-5 (sildenafilo ≥60mg/día o tadalafilo 40mg/día) y riesgo intermedio (CF III WHO y TM6M 165-440m)
- 29% monoterapia con IFD-5 y 71% terapia combinada con ARE
- 3 años desde el diagnóstico de HAP (prevalentes)
- Objetivo primario, evento compuesto de mejoría clínica en la semana 24 (al menos cumple 2) en ausencia de empeoramiento clínico:
  - TM6M incremento 10% o 30m
  - CF I-II WHO
  - Descenso de pro-BNP >30%

Tratamiento HAP. Switch tratamiento. REPLACE



***Lancet Respir Med* 2021**

Algoritmo tratamiento HAP.



Eur Respir J 2022; in press: 2200879
European Heart Journal (2022) 00, 1–114

Trasplante pulmonar en HAP.

Table 20 Criteria for lung transplantation and listing in patients with pulmonary arterial hypertension

Referral
Potentially eligible patients for whom LTx might be an option in case of treatment failure
ESC/ERS intermediate–high or high risk or REVEAL risk score >7 on appropriate PAH medication
Progressive disease or recent hospitalization for worsening PAH
Need for i.v. or s.c. prostacyclin therapy
Known or suspected high-risk variants, such as PVOD or PCH, systemic sclerosis, or large and progressive pulmonary artery aneurysms
Signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications, such as recurrent haemoptysis

Eur Respir J 2022; in press: 2200879
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Tto HAP. Nueva vía terapéutica. Sotatercept

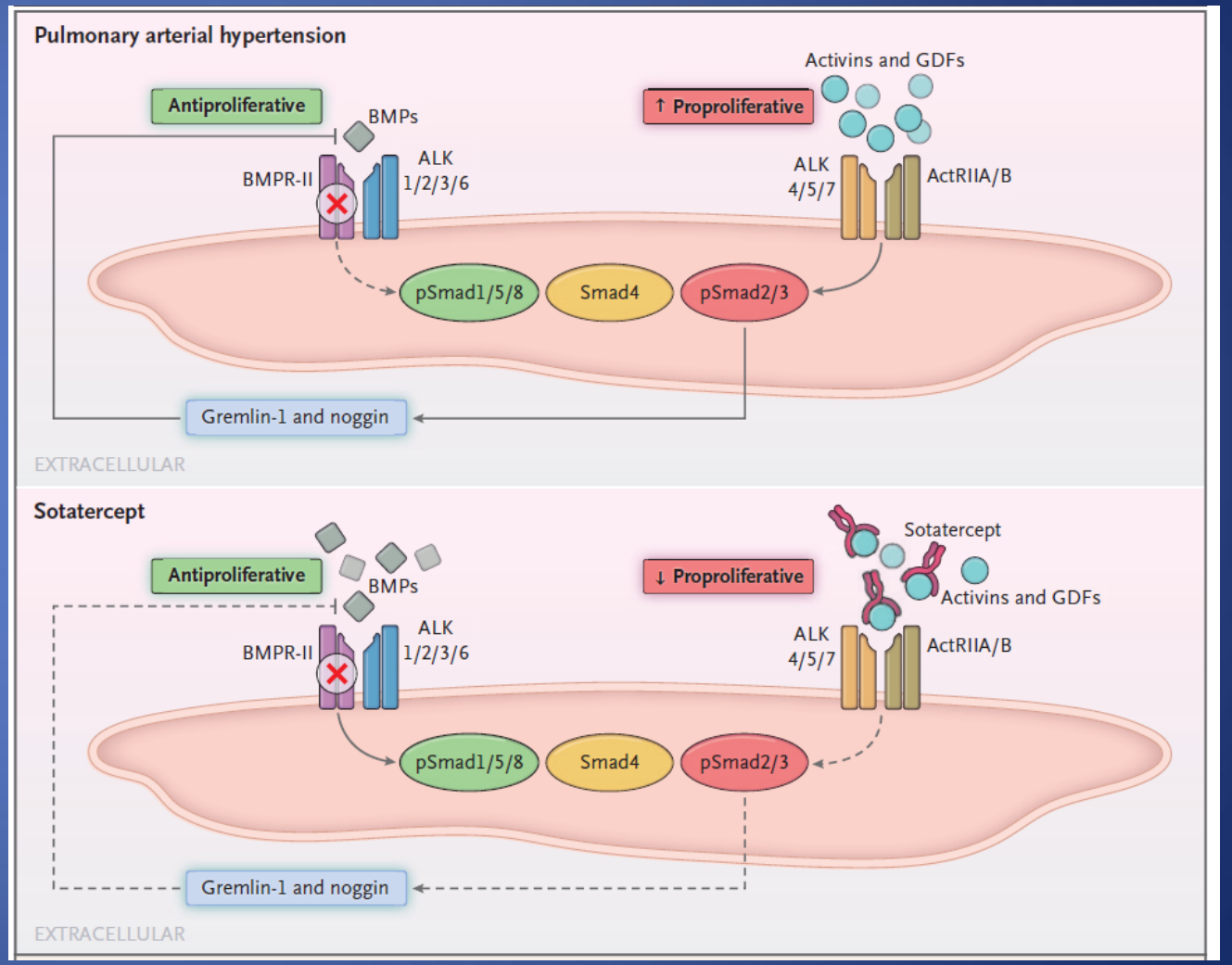
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

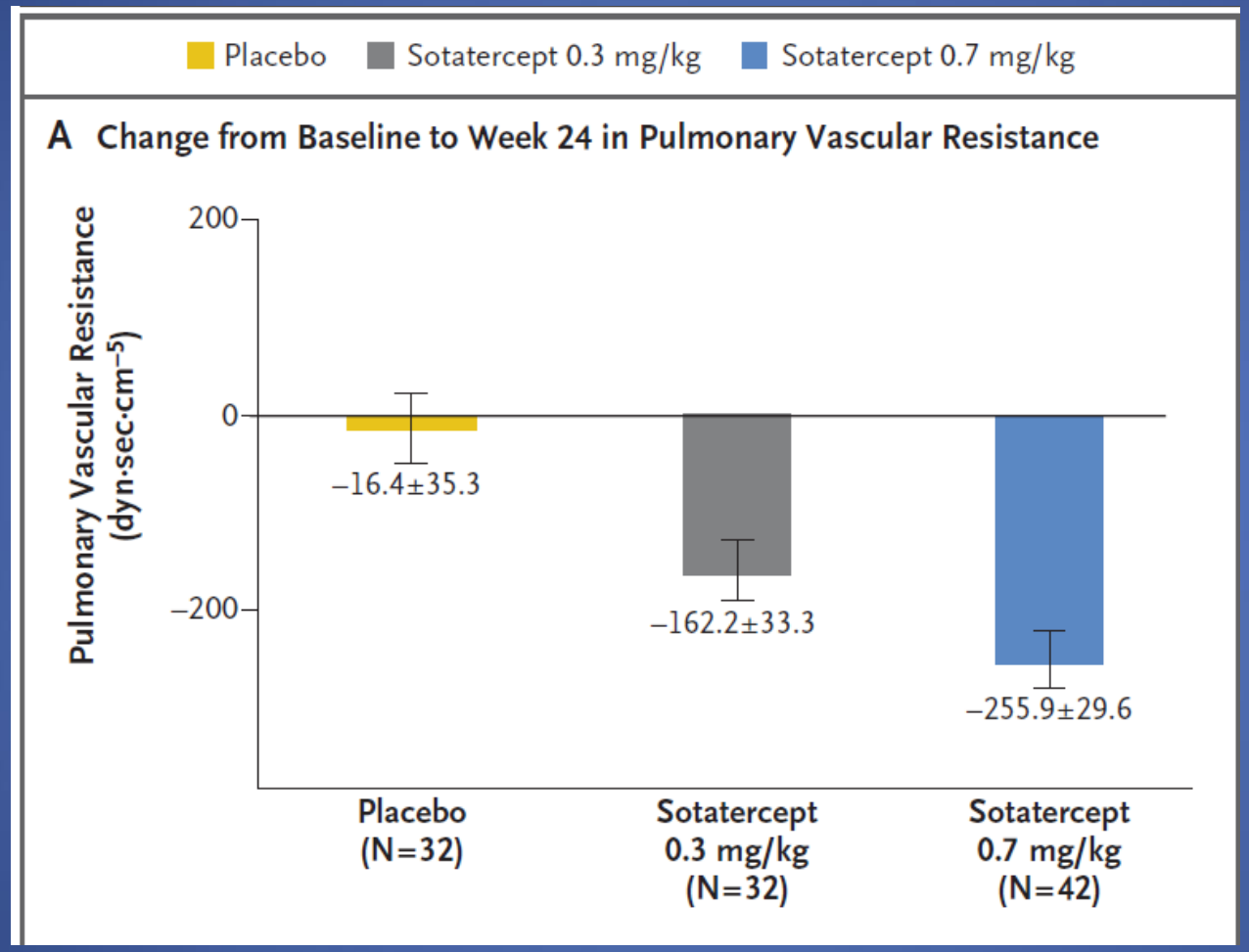
Marc Humbert, M.D., Ph.D., Vallerie McLaughlin, M.D., J. Simon R. Gibbs, M.D., Mardi Gomberg-Maitland, M.D., Marius M. Hoeper, M.D., Ioana R. Preston, M.D., Rogerio Souza, M.D., Ph.D., Aaron Waxman, M.D., Ph.D., Pilar Escribano Subias, M.D., Ph.D., Jeremy Feldman, M.D., Gisela Meyer, M.D., David Montani, M.D., Ph.D., Karen M. Olsson, M.D., Solaiappan Manimaran, Ph.D., Jennifer Barnes, Ph.D., Peter G. Linde, M.D., Janethe de Oliveira Pena, M.D., Ph.D., and David B. Badesch, M.D., for the PULSAR Trial Investigators*

- Administración sc cada 3 semanas
- ECA controlado por placebo.
- 106 pacientes HAP
- Cambio en RVP a 24 semanas



N Engl J Med 2021;384:1204-15.

Tratamiento HAP. Nueva vía terapéutica. PULSAR



N Engl J Med 2021;384:1204-15.

Tto HAP. Nueva vía terapéutica. Sotatercept

The NEW ENGLAND JOURNAL of MEDICINE

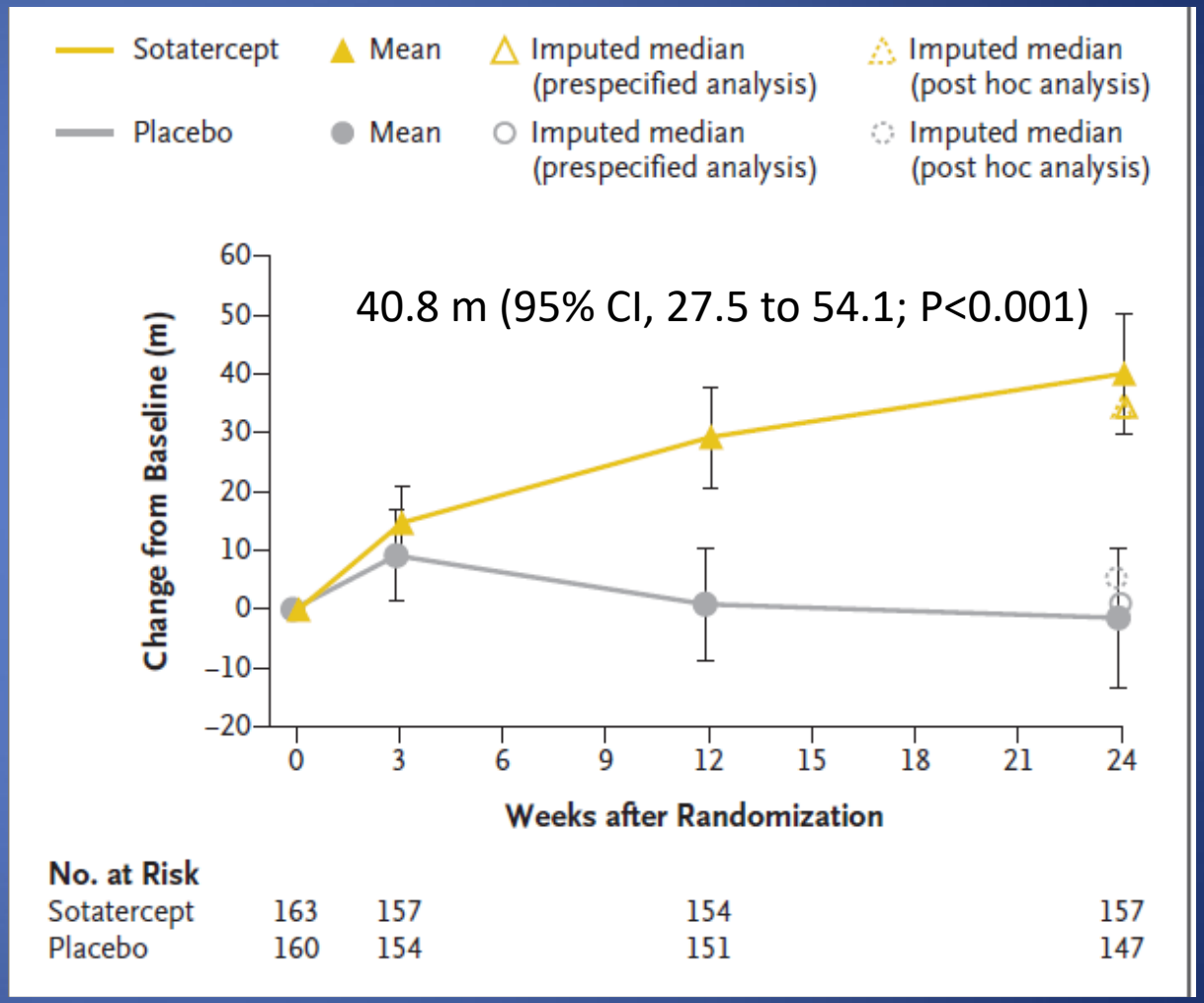
ORIGINAL ARTICLE

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

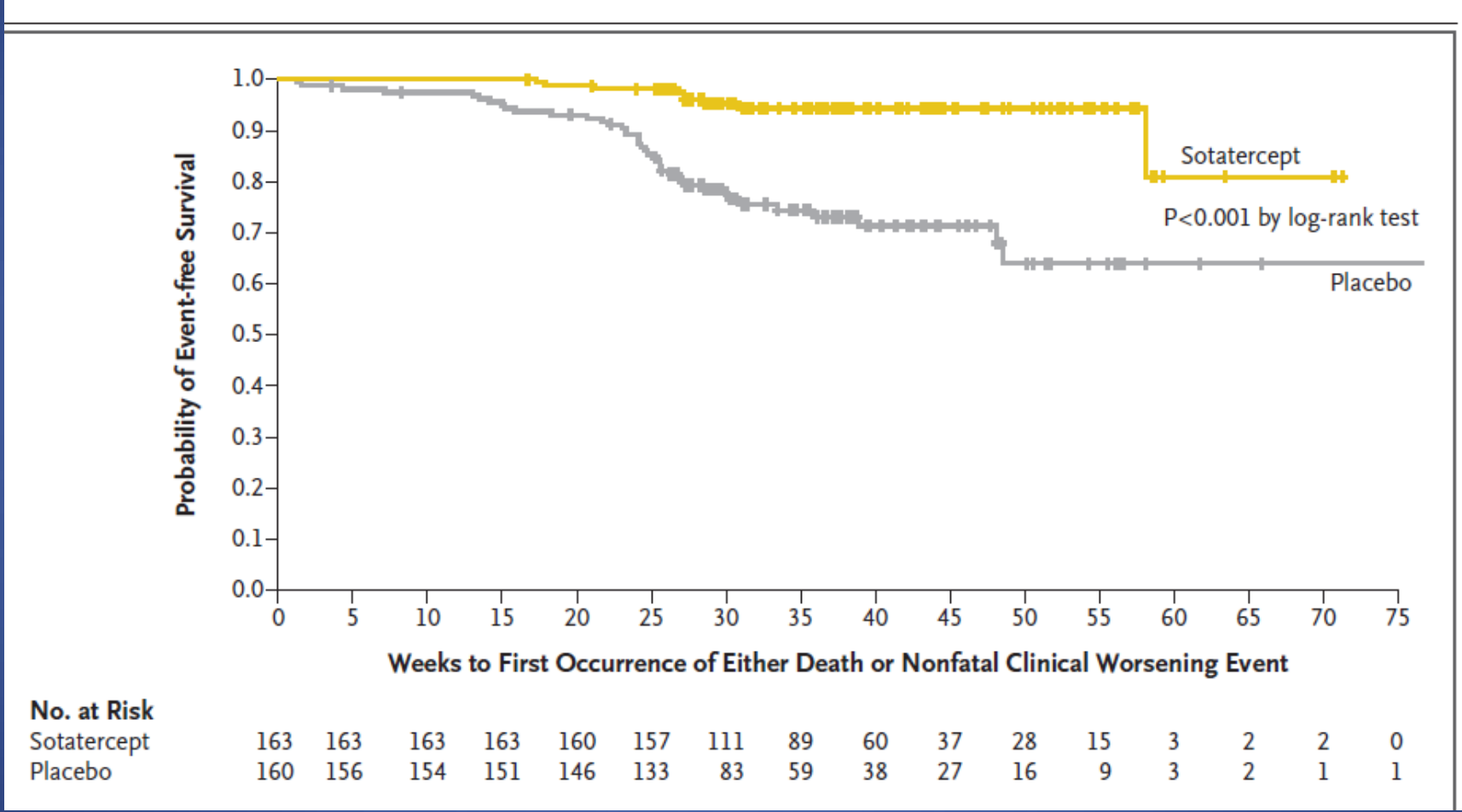
M.M. Hoeper, D.B. Badesch, H.A. Ghofrani, J.S.R. Gibbs, M. Gomberg-Maitland, V.V. McLaughlin, I.R. Preston, R. Souza, A.B. Waxman, E. Grünig, G. Kopeć, G. Meyer, K.M. Olsson, S. Rosenkranz, Y. Xu, B. Miller, M. Fowler, J. Butler, J. Koglin, J. de Oliveira Pena, and M. Humbert, for the STELLAR Trial Investigators*

N Engl J Med 2023;388:1478-90.

- Administración sc cada 3 semanas
- ECA controlado por placebo 1:1.
- 323 pacientes HAP
- 60% en triple terapia
- 40% prostaciclina sistémica
- Cambio en TM6M a 24 semanas



Tto HAP. Nueva vía terapéutica. Sotatercept



N Engl J Med 2023;388:1478-90.

Tto HAP. Nueva vía terapéutica. Imatinib inhalado.

AV-101, a Novel Inhaled Dry Powder Formulation of Imatinib, in Healthy Adult Participants: A Phase 1 Single and Multiple Ascending Dose Study

Hunter Gillies, Ralph Niven, Benjamin T. Dake, Murali M. Chakinala, Jeremy P. Feldman, Nicholas S. Hill, Marius M. Hoeper, Marc Humbert, Vallerie V. McLaughlin, Martin Kankam

Please cite this article as: Gillies H, Niven R, Dake BT, *et al*. AV-101, a Novel Inhaled Dry Powder Formulation of Imatinib, in Healthy Adult Participants: A Phase 1 Single and Multiple Ascending Dose Study. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00433-2022).

- Study of AV-101 (Dry Powder Inhaled Imatinib) in Patients With Pulmonary Arterial Hypertension (PAH) (IMPAHCT), Phase IIb (RVP) y III (TM6M).
- https://clinicaltrials.gov/study/NCT05036135
- https://impahctstudy.com/

Supervivencia era terapéutica

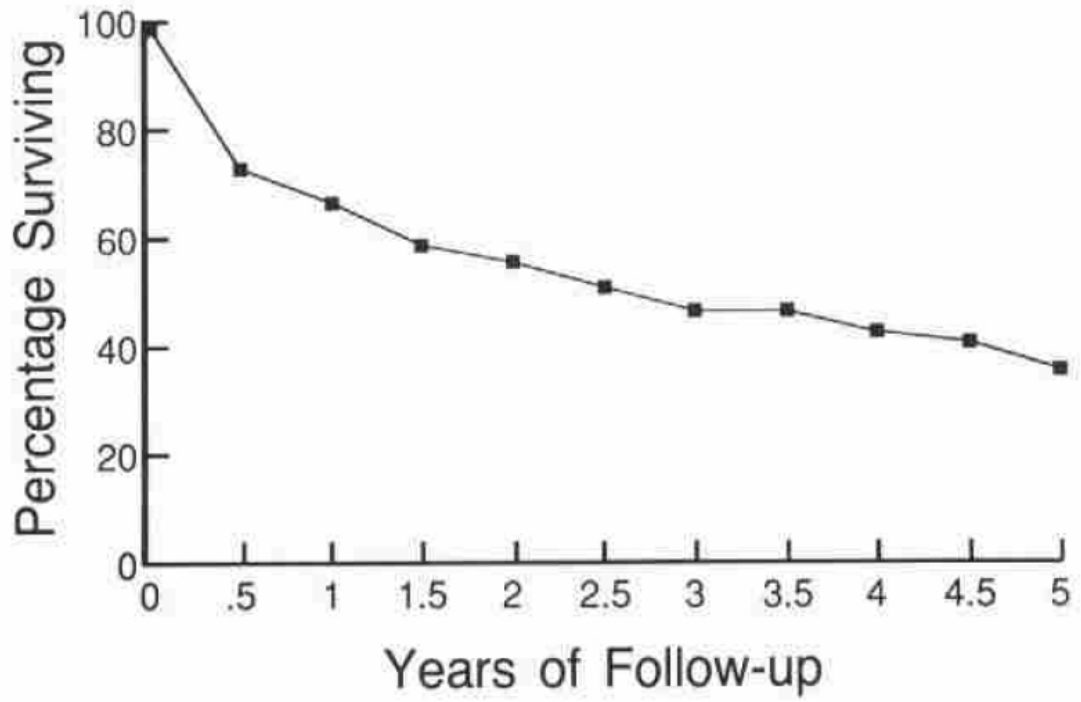
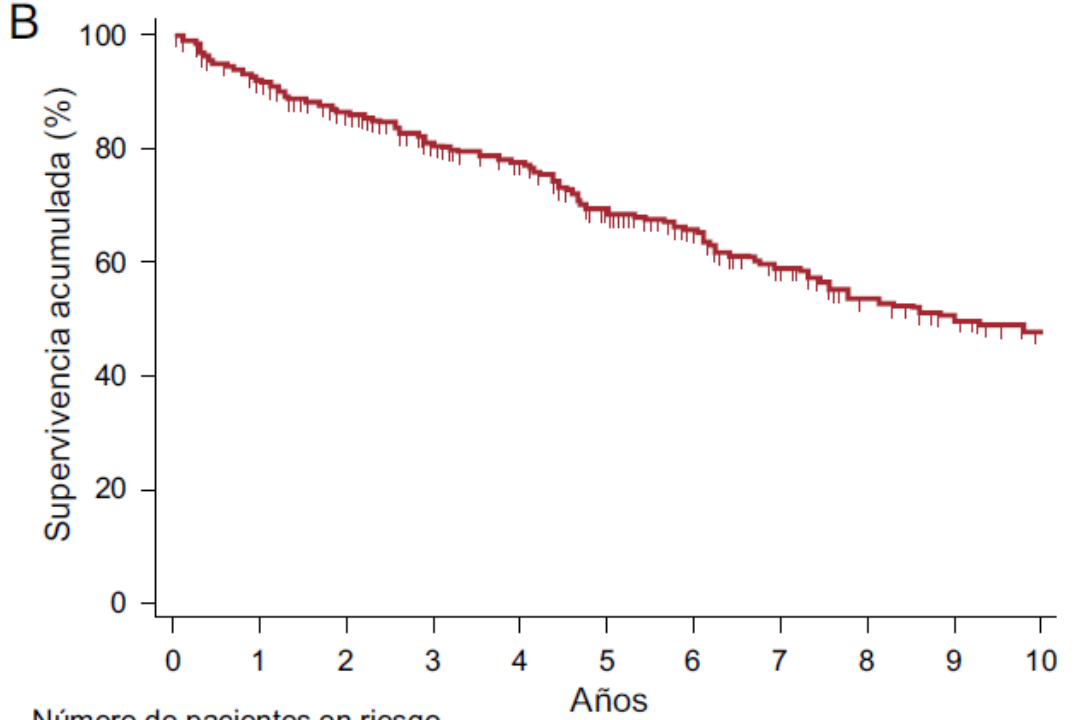


Figure 1. Estimated percentage of patients surviving over time from the baseline catheterization. Number of patients at risk are shown for 0 through 5 years. Median survival is estimated at 2.8 years. Estimated percentages of patients surviving at 1, 3, and 5 years are 68%, 48%, and 34%, respectively.

Annals of Internal Medicine. 1991;**115**:343-349.



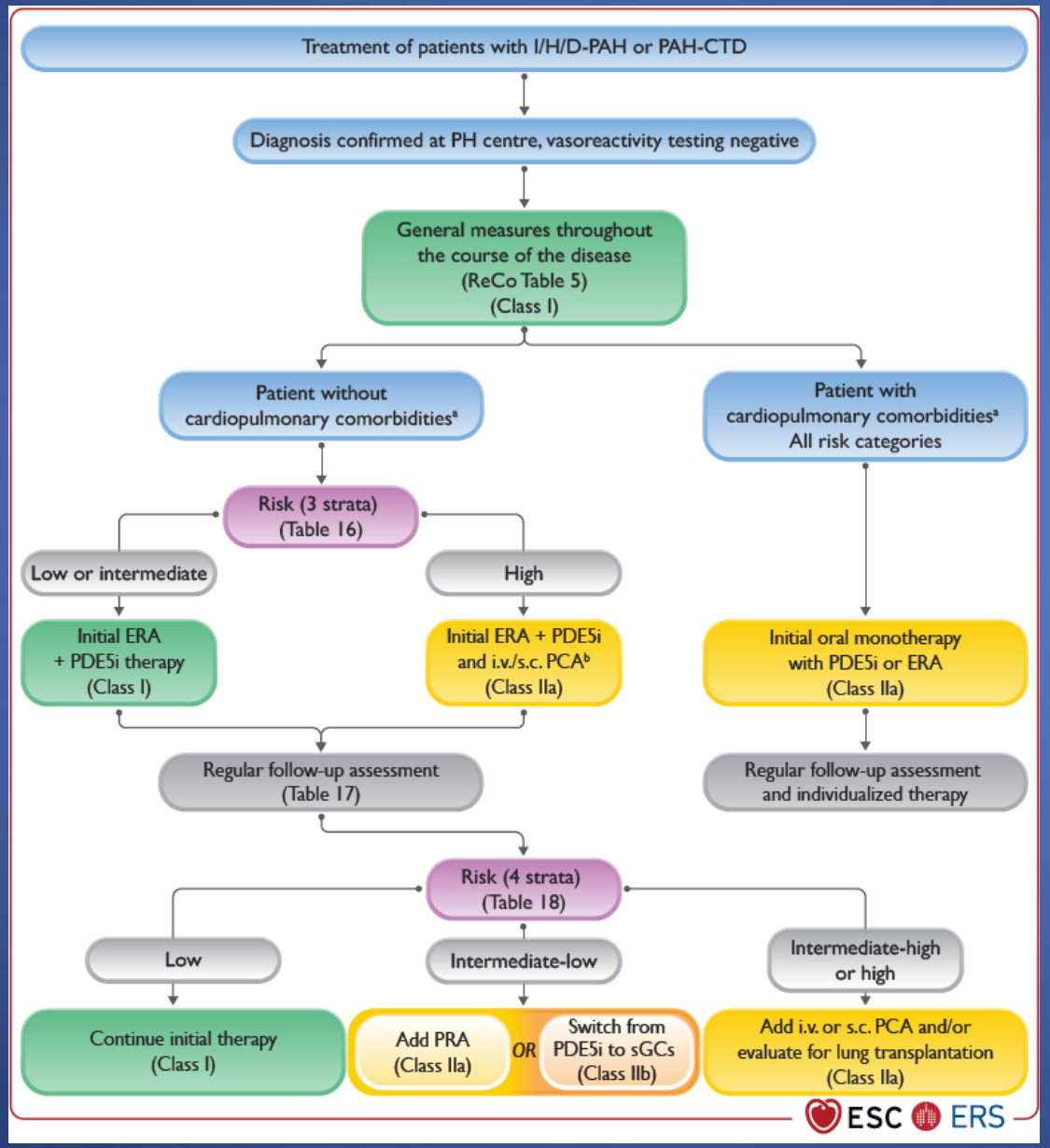
Número de pacientes en riesgo

	379	335	291	250	225	182	151	122	99	87	67

SG (%)	0	1	2	3	4	5	6	7	8	9	10
Global	100,0	92,2	86,2	80,6	77,6	68,5	65,3	59,0	53,8	50,5	48,0

Quezada-Loaiza CA. Rev Esp Cardiol. 2017;70(11):915–923

Conclusiones.



HAY VIDA FUERA DE LA VÍA ENDOTELIAL

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